

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07J 15/00, A61K 31/565, C07J 53/00		A1	(11) International Publication Number: WO 00/53619 (43) International Publication Date: 14 September 2000 (14.09.00)
(21) International Application Number: PCT/EP00/01755		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 2 March 2000 (02.03.00)			
(30) Priority Data: 99200665.0 8 March 1999 (08.03.99) EP			
(71) Applicant (<i>for all designated States except US</i>): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 Arnhem (NL).			
(72) Inventors; and		Published	
(75) Inventors/Applicants (<i>for US only</i>): LOOZEN, Hubert, Jan, Jozef [NL/NL]; Meerhoek 602, NL-5403 AC Uden (NL). LEYSEN, Dirk [BE/BE]; Kerkstraat 26, B-3920 Lommel (BE). VAN DER LOUW, Jaap [NL/NL]; Pauwoog 12, NL-5345 EN Oss (NL).			
(74) Agent: KRAAK, Hajo; P.O. Box 20, NL-5340 BH Oss (NL).			
(54) Title: 14.BETA., 17-ALPHA-HYDROXYMETHYLANDROSTANE DERIVATIVES AS ANDROGENS			
(57) Abstract			
<p>The disclosed invention relates to the unexpected finding of steroids for use as androgens which are characterized by a configuration opposite to that of natural steroids, viz. 14α, 17β. These steroids according to the invention are $(14\beta, 17\alpha)$-17-(hydroxymethyl) steroids, and they are found to have in common an androgenic activity. They can be used for the preparation of an agent for male contraception, as well as for the preparation of a medicament for the treatment of androgen insufficiency.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

14. BETA., 17-ALPHA-HYDROXYMETHYLROSTANE DERIVATIVES AS ANDROGENS

The invention is in the field of steroid hormones. This is a relatively old field, in which a great many possible substitutions on a common steroid skeleton are known to lead to many different 5 hormonal activities and medical utilities, and in which the basic structure-activity relations seemed to be known. Surprisingly, in this well-investigated field, a completely new discovery led to the present invention, according to which novel androgens are provided.

Natural steroid hormones, such as testosterone and estradiol, have the configuration 14 α and 10 17 β . The invention now resides in the unexpected finding of novel steroids which are characterised by the opposite configuration, viz. 14 β ,17 α . These steroids according to the invention are (14 β ,17 α)-17-(hydroxymethyl) steroids, and they are found to have in common an androgenic activity. A medical use of such compounds has not been known in the art. The 15 compounds only figure in disclosures on intermediates in the partial synthesis of aldosterone, see Barton, D.H. *et al*, J.Chem.Soc., No. 6 of 1957, 2698-2706 (1957) and Da Silva Campos Neves, A. Chemical Abstracts 53, no 12., abstract no. 1442a (1959).

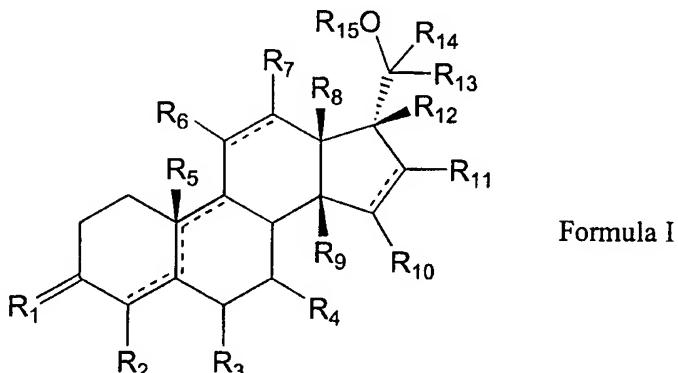
The invention thus pertains to these steroids for use as a medicine. The invention also pertains to pharmaceutical formulations comprising any or more of such steroids together with 20 pharmaceutically acceptable auxiliaries. A proviso is made in that carbon atom number 11 of the steroid skeleton does not carry, as a substituent, a homocyclic or heterocyclic aryl group. The latter disclaimer is made on the basis of EP 277 676. This disclosure pertains to anti-progestagens having an 11-aryl substituent, which is typical for steroids having that activity. Incidentally, in two examples a mixture of two compounds having different steric 25 configurations is prepared, a component in the mixture being a compound having a 14 β ,17 α configuration.

The above compounds of the invention are well characterised with reference to the requirement that they have a 17-hydroxymethyl group, and that the configuration be 14 β and 17 α . In other 30 words, the exact nature of any optional substituents at any carbon atom of the steroid skeleton, or at any substituent group, is not particularly critical to the invention. The person of ordinary

skill in the art of steroid chemistry is well aware of which substituents are practically applicable.

It should be noted that in the past steroids having the abnormal $14\beta,17\alpha$ configuration received some attention in the art of organic chemistry. See e.g. the more than thirty years old publication of Crabbé, P. et al, Can. J. Chem. 46, 349 (1967). This document incidentally mentions one ($14\beta,17\alpha$)-17-(hydroxymethyl) steroid, viz. 20-hydroxy- $14\beta,17\alpha$ -19-norpregn-4-en-3-one as a chemical intermediate. Similarly, other ($14\beta,17\alpha$)-17-(hydroxymethyl) steroids known as chemical compounds *per se*, are ($3\beta,5\alpha,14\beta,17\alpha$)-pregna-3,20-diol and ($3\beta,14\beta,17\alpha$)-pregna-5,9(11)-diene-3,20-diol, see Shoppee CW et al, Helv. Chim. Acta, 27, 246 (1944) and J. Chem. Soc., 3610 (1962), and ($14\beta,17\alpha$)-20-hydroxy-19-norpregn-4-en-3-one, see Crabbe P et al, Can. J. Chem., 46, 349 (1968). To the extent that the invention pertains to chemical compounds, these known compounds are disclaimed here.

The invention particularly pertains to steroids which satisfy structural formula I given below, or pharmaceutically acceptable salts or esters, prodrugs and precursors thereof.



wherein

- 20 R₁ is O, (H,H), (H,OR), NOR, with R being hydrogen, (C₁₋₆) alkyl, (C₁₋₆) acyl;
- R₂ is hydrogen, (C₁₋₆) alkyl, or halogen;
- R₃ is hydrogen, (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl;
- R₄ is hydrogen, halogen, or cyano; or R₄ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;
- 25 R₅ is hydrogen, or (C₁₋₆) alkyl;

R₆ is hydrogen, (C₁₋₆) alkoxy, or halogen; or R₆ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl, a (C₁₋₆) alkylidene group, or a (C₂₋₆) alkenylidene group, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₇ is hydrogen, or (C₁₋₆) alkyl;

5 R₈ is (C₁₋₆) alkyl;

R₉ is hydrogen, halogen or cyano; or R₉ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₁₀ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₀ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or R₁₀

10 together with R₁₁ and the carbon atoms at which they are placed form a cyclopropane ring;

R₁₁ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₁ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or R₁₁ together with R₁₀ and the carbon atoms at which they are placed form a cyclopropane ring;

R₁₂ is hydrogen, hydroxy, halogen, or cyano; or R₁₂ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl,

15 each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₁₃ and R₁₄ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, (C₁₋₄) alkoxy, (C₁₋₄) alkyl or halogen; or R₁₃ and R₁₄ are independently (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₃₋₆) cycloalkyl, (C₅₋₆) cycloalkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, phenyl, oxo, halogen, or cyano; or R₁₃ and R₁₄ together with the

20 carbon atom at which they are placed form a (C₃₋₆) cycloalkane ring or a (C₅₋₆) cycloalkene ring;

R₁₅ is hydrogen, SO₃H, (C₁₋₆) alkyl, (C₁₋₁₅) acyl; and

the dotted lines indicate optional bonds.

25 The term (C₁₋₆) alkyl as used in the definition of formula I means a branched or unbranched alkyl group having 1-6 carbon atoms, like methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, and hexyl. Likewise, the term (C₁₋₄) alkyl means an alkyl group having 1-4 carbon atoms. Preferred alkyl groups have 1-4 carbon atoms, and most preferred alkyl groups are methyl and ethyl.

The term (C_{2-6}) alkenyl means a branched or unbranched alkenyl group having at least one double bond and 2-6 carbon atoms. Preferred alkenyl groups have 2-4 carbon atoms, such as vinyl and propenyl.

5 The term (C_{2-6}) alkynyl means a branched or unbranched alkynyl group having at least one triple bond and 2-6 carbon atoms. Preferred alkynyl groups have 2-4 carbon atoms, such as ethynyl and propynyl.

10 The term (C_{1-6}) alkylidene means a branched or unbranched alkylidene group having 1-6 carbon atoms. Preferred alkylidene groups have 1-4 carbon atoms, and most preferred is methylene.

The term (C_{2-6}) alkenylidene means a branched or unbranched alkenylidene group having 2-6 carbon atoms. Preferred alkenylidene groups have 2-4 carbon atoms, such as ethenylidene.

15

The term (C_{3-6}) cycloalkyl or (C_{3-6}) cycloalkane ring means a cycloalkane ring having 3-6 carbon atoms, like cyclopropane, cyclobutane, cyclopentane and cyclohexane.

20 The term (C_{5-6}) cycloalkenyl or (C_{5-6}) cycloalkene ring means a cycloalkene ring having at least one double bond and 5 or 6 carbon atoms.

25 The term (C_{1-6}) alkoxy means a branched or unbranched alkoxy group having 1-6 carbon atoms, like methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butyloxy, pentyloxy, and hexyloxy. Likewise, the term (C_{1-4}) alkoxy means a branched or unbranched alkoxy group having 1-4 carbon atoms. Preferred alkoxy groups have 1-4 carbon atoms, and most preferred is methoxy.

30 The term (C_{1-15}) acyl means an acyl group derived from a carboxylic acid having from 1-15 carbon atoms, like formyl, acetyl, propanoyl, butyryl, 2-methylpropanoyl, pentanoyl, pivaloyl, hexanoyl, and so on. Also included within the definition of (C_{1-15}) acyl are [(C_{3-6}) cycloalkyl]carbonyl,

- [(C₅₋₆) cycloalkenyl]carbonyl,
benzoyl,
[[(C₁₋₁₂) alkyl](C₃₋₆) cycloalkyl]carbonyl,
[[(C₂₋₁₂) alkenyl](C₃₋₆) cycloalkyl]carbonyl],
5 [[(C₂₋₁₂) alkynyl](C₃₋₆) cycloalkyl]carbonyl],
[[(C₁₋₁₀) alkyl](C₅₋₆) cycloalkenyl]carbonyl],
[[(C₂₋₁₀) alkenyl](C₅₋₆) cycloalkenyl]carbonyl],
[[(C₂₋₁₀) alkynyl](C₅₋₆) cycloalkenyl]carbonyl],
(C₁₋₉) alkylbenzoyl,
10 (C₂₋₉) alkenylbenzoyl,
(C₂₋₉) alkynylbenzoyl.

Also included within the definition of (C₁₋₁₅) acyl are acyl groups derived from dicarboxylic acids, like hemi-maloyl, hemi-succinoyl, hemi-glutaroyl, and so on. Preferred is hemi-succinoyl.

15

The term halogen means fluorine, chlorine, bromine, or iodine. When halogen is a substituent at an alkyl group, like in the definition R₂, R₄, R₆, R₉₋₁₄, Cl and F are preferred, F being most preferred.

- 20 It is understood that the (14β,17α)-17-(hydroxymethyl) steroid derivatives of the invention have the natural configurations 5α, 8β, 9α, 10β, 13β.

The (14β,17α)-17-(hydroxymethyl) steroid derivatives of this invention have the natural configurations 5α, 8β, 9α, 10β, 13β, and possess also one or more additional chiral carbon atoms. The compounds may therefore be obtained as a pure diastereomer, or as a mixture of diastereomers. Methods for obtaining the pure diastereomers are well known in the art, *e.g.* crystallization or chromatography.

- 30 For therapeutic use, salts of the compounds of formula I are those wherein the counterion is pharmaceutically acceptable. However, salts of the acids according to formula I [*i.e.* compounds wherein R₁ is (H,OSO₃H) or wherein R₁₅ is SO₃H] may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts,

whether pharmaceutically acceptable or not, are included within the ambit of the present invention. Examples of salts of acids according to the invention are mineral salts such as sodium salt, potassium salt, and salts derived from organic bases like ammonia, imidazole, ethylenediamine, triethylamine and the like.

5

The compounds of the invention as described hereinbefore in general possess an unexpected androgenic activity. Androgenic activity can be measured in various ways. Thus, the potency of androgens can be determined *in vitro* using the cytoplasmic androgen receptor from human breast tumor cells (MCF-7 cell line); see Bergink, E.W. *et al*, *Comparison of the receptor binding properties of nandrolone and testosterone under in vitro and in vivo conditions*, J. Steroid Biochem. 22, 831-836 (1985). It is also possible to use Chinese hamster ovary (CHO) cells transfected with the human androgen receptor (incubation time 16 h, temperature 4 °C) and compared with the affinity of 5α-dihydrotestosterone [according to the procedure described by Bergink, E.W. *et al*, J. Steroid Biochem. 19, 1563-1570 (1983)]. The transactivative androgen activity of the compounds of the invention can be measured, e.g. in Chinese hamster ovary cells (CHO) transfected with the human androgen receptor (hAR), in combination with a mouse mammary tumor virus (MMTV), and luciferase receptor gene (incubation time 16 h, temperature 37 °C) and compared with the activity of 5α-dihydrotestosterone [according to the procedure described by Schoonen, W.G.E.J. *et al*, Analyt. Biochem. 261, 222-224 (1998)]. For the *in vivo* potency determination of androgens the classical Hershberger test can be used. In this test the androgenic (increase in prostate weight) and anabolic activities [increase of the musculus levator ani (MLA)] of a compound are tested in immature castrated rats after daily administration for 7 days; see Hershberger, L.G. *et al*, *Myotrophic activity of 19-Nortestosterone and other steroids determined by modified levator ani muscle method*, Proceedings of the society for experimental biology and medicine 83, 175-180 (1953). Additionally, the effect of an androgenic compound on LH suppression can be tested in mature castrated rats according to Kumar, N. *et al*, *The biological activity of 7alpha-methyl-19-nortestosterone is not amplified in male reproductive tract as is that of testosterone*, Endocrinology 130, 3677-3683 (1992).

30

The preference goes to those compounds according to the invention which exhibit a relatively high androgenic activity. Thus, the preferred compounds of the invention are those satisfying the above structural formula I, wherein:

- R₁ is O;
- 5 R₂, R₃, R₅, R₆, R₇, R₉, R₁₀, R₁₁, R₁₂, and R₁₄ all are hydrogen;
- R₄ is H or methyl;
- R₈ is methyl;
- R₁₃ is hydrogen, or C₁₋₂ (alkyl) with the configuration at carbon atom no. 20 being S;
- R₁₅ is H or (C₁₋₁₅) acyl;
- 10 and wherein a double bond is present between carbon atoms nos. 4 and 5, and optionally also between carbon atoms nos. 9 and 10.

As androgenic hormones the (14 β ,17 α)-17-(hydroxymethyl) steroids of the present invention can be used in, int.al., male contraception and male HRT (hormone replacement therapy).

- 15 Thus, e.g. male contraception may comprise a regimen of administration of hormones in which a progestagen serves to achieve a contraceptive effect and an androgen serves to supplement the resulting decreased testosterone level. Another option is that male contraception is performed with an androgenic hormone alone. The androgens can also be used for androgen supplementation in the partially androgen deficient ageing male. Next to the use in the male,
- 20 the androgens of the invention also can be used in the female, e.g. as androgen replacement therapy in postmenopausal women.

- The present invention also relates to a pharmaceutical composition comprising a steroid compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such
- 25 as described in the standard reference, Gennaro *et al*, *Remmington's Pharmaceutical Sciences*, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). The mixture of the steroid compounds according to the invention and the pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically
- 30 suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the

like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The steroid compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

5

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

Furthermore, the invention relates to the use of the steroid compound according to the
10 invention for the manufacture of a medicament in the treatment of androgen-deficiency, such as in male or female HRT (hormone replacement therapy). Accordingly, the invention also includes a method of treatment in the field of male or female HRT, comprising the administration to a male or female patient suffering from an androgen-deficiency, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

15

Further, the invention relates to the use of a steroid compound according to the invention for the manufacture of a medicament having contraceptive activity (for which in the art the term "contraceptive agent" is also used). Thus the invention also pertains to the medical indication of contraception, *i.e.* a method of contraception comprising the administration to a subject,
20 being a male, preferably a human male, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form), in combined therapy with a progestagen or not.

The androgens according to the invention can also be used in a kit for male contraception. Although this kit can comprise one or more androgens only, it is preferred that it comprises
25 means for the administration of a progestagen and means for the administration of an androgen. The latter means is a pharmaceutical formulation comprising compound according to the invention as described hereinbefore, and a pharmaceutically acceptable carrier.

The invention also pertains to a method of treatment comprising administering to a (notably
30 human) male or female in need of androgen-supplementation a therapeutically effective amount of a (14 β ,17 α)-17-(hydroxymethyl) steroid as described hereinbefore. This is

irrespective of whether or not the need for androgen-supplementation has arisen as a result of male contraception involving the administration of a sterilitant, such as a progestagen.

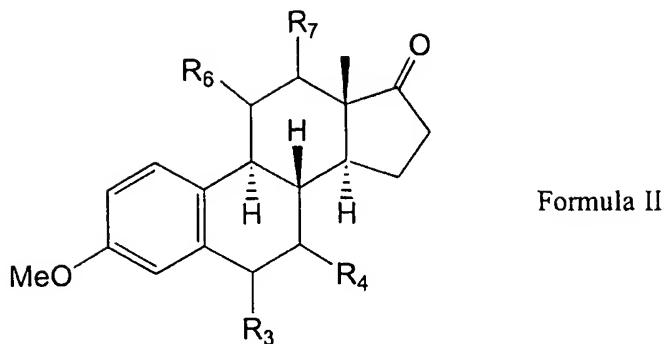
Further, the invention pertains to a method of contraception, comprising administering to a
5 fertile male, notably human, a (14 β ,17 α)-17-(hydroxymethyl) steroid as described hereinbefore in a dosage amount and regimen which is sufficient for said compound to be contraceptively effective *per se*. Alternatively, the method of contraception provided by the present invention comprises administering to a fertile male, notably human, a contraceptively effective combination of a sterilitant, such as a progestagen, and a (14 β ,17 α)-17-(hydroxymethyl)
10 steroid as described hereinbefore.

The compounds of the invention may be produced by various methods known in the art of organic chemistry in general, and especially in the art of the chemistry of steroids (see, for example: Fried, J. *et al*, *Organic Reactions in Steroid Chemistry*, Volumes I and II, Van
15 Nostrand Reinhold Company, New York, 1972).

Crucial is the synthesis of steroids of inverted stereochemistry at C-14 (14 β -configuration) and possessing a (substituted) 17 α -hydroxymethyl group.

A convenient starting material for the preparation of compounds of formula I wherein R₁ is
20 oxo; R₂, R₅, R₉, R₁₀, R₁₁, R₁₂ and R₁₅ are hydrogen; R₃, R₄, R₆ and R₇ are hydrogen or (C₁₋₆) alkyl; R₈ is methyl; R₁₃ and R₁₄ have the previously given meaning; and the dotted lines indicate a Δ⁴ double bond, is for instance a compound of general formula II, wherein R₃, R₄, R₆ and R₇ are hydrogen or (C₁₋₆) alkyl, whose synthesis is known in literature, or which can be prepared using standard methods.

10



Formula II

A possible synthesis route starts with the transformation of compounds of formula II to the corresponding 14 β -derivatives. A 3-methoxyestra-1,3,5(10)-trien-17-one can be converted to a 5 cyclic 1,2-ethanediyl acetal which can then be brominated to afford a (16 α)-16-bromo-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal derivative. Bromination can be accomplished using pyridinium tribromide, phenyltrimethylammonium tribromide or other brominating agents known in the art [Rasmussen, G.H. *et al*, Steroids 22, 107 (1973)]. The 16 α -bromo compound is dehydrobrominated by reaction with a base, *e.g.* potassium *tert*-butoxide 10 in xylene or dimethyl sulfoxide, to give the Δ^{15} compound [Johnson, W.S. *et al*, J. Am. Chem. Soc. 79, 2005 (1957); Poirier, D. *et al*, Tetrahedron 47, 7751 (1991)]. Mild hydrolysis of the ethylene ketal, for instance by treatment with *p*-toluenesulfonic acid in a mixture of acetone 15 and water [Johnson, *supra*], results in a 3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative which is then converted to a 3-methoxyestra-1,3,5(10),14,16-pentaen-17-ol acetate by acid-catalyzed reaction with acetic anhydride, isopropenyl acetate or other acetylating agents [Rasmussen, *supra*; Bull, J.R. *et al*, J. Chem. Soc., Perkin Trans. I, 241 (1990)]. The acetate is treated with sodium borohydride or other reducing agents [Rasmussen, *supra*] to result in the formation of a (17 β)-3-methoxyestra-1,3,5(10),14-tetraen-17-ol derivative. The Δ^{14} double bond is hydrogenated, for instance by using palladium on activated carbon [Schubert, G. *et al*, Z. Chem. 23, 410 (1983)], whereafter oxidation of the resulting (14 β ,17 β)-3-methoxyestra-1,3,5(10)-trien-17-ol derivative results in the formation of a (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative (for oxidations, see Hudlicky, M., *Oxidations in Organic Chemistry*, ACS Monograph 186, Washington, DC, 1990). A 3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative can also be subjected to acid-catalyzed isomerization to produce a mixture of (14 β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one and 3-methoxyestra-1,3,5(10),14-tetraen-17-one derivatives which can be hydrogenated as described above to a (14 β)-3-methoxyestra-

1,3,5(10)-trien-17-one derivative. Alternatively, they can be separated after which the (14 β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative can be converted by 1,4-reduction to the (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one.

A (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative can also be obtained as follows: a 3-

5 methoxyestra-1,3,5(10)-trien-17-one derivative is brominated directly, for instance by reaction with copper(II) bromide in benzene/methanol [Segaloff, A. *et al*, Steroids 22, 99 (1973)], or by reaction of the corresponding enol acetate with bromine [Johnson, *supra*], to produce a 16 α -bromoketone derivative. Dehydrobromination, e.g. by reaction with LiBr/Li₂CO₃/DMF [Bull, 10 *supra*], usually results in a mixture of (14 β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one and 3-methoxyestra-1,3,5(10),14-tetraen-17-one derivatives which can be processed as described above.

Alternative methods to introduce a Δ^{15} double bond include: conversion of a 3-methoxyestra-1,3,5(10)-trien-17-one to the corresponding enol silyl ether or enol acetate and reaction with a palladium(II) salt [Bull, J.R. *et al*, J. Chem. Soc., Perkin Trans. I, 1269 (1996); Takahashi, T. 15 *et al*, Tetrahedron 41, 5747 (1985)] or reaction of the enolate with methyl 2-pyridinesulfinate [Dionne, P. *et al*, Steroids 62, 674 (1997)].

A (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative thus obtained can now be converted to a (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-methanol derivative. The conversion of 17-oxo to 17 α -CH₂OH can be accomplished in several ways:

- (a) 1: Wittig or Peterson reaction to a (14 β)-3-methoxy-17-methyleneestra-1,3,5(10)-triene derivative [Maercker, A., in Org. Reactions 14, p. 270, Wiley, New York, 1965; Ager, D.J., in Org. Reactions 38, p. 1, Wiley, New York, 1990]; 2: hydroboration, for instance by use of 9-BBN, disiamylborane, or thexyborane [see e.g. Zweifel, G. *et al*, in Org. Reactions 13, p. 1, Wiley, New York, 1963], resulting in the formation of a (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-methanol derivative.
- (b) 1: Conversion of the 17-ketone to a (14 β ,17 α)-3-methoxyspiroestra-1,3,5(10)-triene[17,2']oxirane by reaction with e.g. trimethylsulfonium iodide/n-BuLi [Corey, E.J. *et al*, J. Am. Chem. Soc. 87, 1353 (1965)]; 2: (Lewis)acid-catalyzed isomerization of the 17 α -oxirane to 17 α -formyl [Rickborn, B., in Comprehensive Organic Synthesis, Vol. 3, p. 733, Pergamon Press, Oxford, New York (1991)]; 3: reduction of 17 α -formyl to 17 α -CH₂OH.

(c) 1: Conversion of the 17-ketone to a 17-methylene compound; 2: epoxidation with e.g. a peroxy acid, such as *m*-chloroperbenzoic acid, to a (14 β ,17 α)- and/or (14 β ,17 β)-3-methoxyspiroestra-1,3,5(10)-triene[17,2']oxirane; 3: (Lewis)acid-catalyzed isomerization of the 17-oxirane to 17-formyl as described under (b); 4: reduction of 17-formyl to 17-CH₂OH.

5 (d) 1: Conversion of the 17-ketone to a 17 α - or 17 β -oxirane as described under (b) and (c); 2: Lewis acid-catalyzed reduction to the 17-methanol steroid [using e.g. NaBH₃CN/BF₃.Et₂O, see: Tone, H. *et al*, Tetrahedron Lett. 28, 4569 (1987)].

10 (e) 1: Reaction of the 17-ketone to the 17-cyano steroid by reaction with tosylmethyl isocyanide [TosMIC, see Bull, J.R. *et al*, Tetrahedron 31, 2151 (1975)]; 2: reduction of the cyano group to formyl by diisobutylaluminum hydride; 3: reduction of the 17-formyl group to 17-CH₂OH.

(f) 1: Wittig condensation with (Ph)₃P=CHOMe; 2: hydrolysis of the resulting enol ether; 3: reduction of 17-formyl to 17-CH₂OH.

15 (g) 1: Conversion of the 17-ketone to a 17 α - or 17 β -oxirane as described under (b) and (c); 2: elimination to a (14 β)-3-methoxyestra-1,3,5(10),16-tetraene-17-methanol derivative; 3: hydrogenation of the Δ^{16} double bond.

20 (h) 1: Conversion of the 17-ketone to the corresponding enol triflate [see e.g. Cacchi, S. *et al*, Tetrahedron Lett. 25, 4821 (1984)]; 2: palladium-catalyzed alkoxy carbonylation of the latter to a alkyl (14 β)-3-methoxyestra-1,3,5(10),16-tetraene-17-carboxylate [Cacchi, S. *et al*, Tetrahedron Lett. 26, 1109 (1985)]; 3: reduction of the latter to the corresponding (14 β)-3-methoxyestra-1,3,5(10),16-tetraene-17-methanol derivative; 4: hydrogenation of the Δ^{16} double bond.

25 (i) 1: Conversion of the 17-ketone to a alkyl (14 β)-3-methoxyestra-1,3,5(10),16-tetraene-17-carboxylate as described under (h); 2: 1,4-reduction, e.g. by hydrogenation or by lithium or sodium in liquid ammonia, to a alkyl (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-carboxylate derivative; 3: reduction of the ester to 17-CH₂OH.

Some of these methods (a,b,c,e,g) result in the stereoselective formation of the 17 α -CH₂OH isomer. Others (d,f,h,i) may give mixtures which can be separated by chromatography or crystallization.

30

Birch reduction of the (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-methanol derivatives thus obtained [Caine, D. in Org. Reactions 23, p. 1, Wiley, New York, 1976] and hydrolysis of the

resulting $(14\beta,17\alpha)$ -3-methoxyestra-2,5(10)-diene-17-methanol derivative then provides a $(14\beta,17\alpha)$ -17-(hydroxymethyl)estr-4-en-3-one derivative of the invention.

5 Optionally, a $(14\beta,17\alpha)$ -3-methoxyestra-1,3,5(10)-triene-17-methanol derivative can be oxidized as described above to the corresponding 17-carboxaldehyde. The aldehyde can be reacted with an (organometallic) compound of formula $R_{13}M$ in which R_{13} has the previously given meaning except for hydrogen, any functional groups present in R_{13} being suitably protected, and M is Li, Na, K, MgX, ZnX, CeX₂, SiR₃ or SnR₃, to produce a $(14\beta,17\alpha)$ -3-methoxy-17-($CHR_{13}OH$)estra-1,3,5(10)-triene which is usually a mixture of C-20 epimers. The 10 latter can be separated whereafter Birch reduction and hydrolysis as described above and removal of any protecting groups still present provides the $(14\beta,17\alpha)$ -17-($CHR_{13}OH$)estr-4-en-3-one derivatives of the invention in which R_{13} has the previously given meaning except for hydrogen.

15 Optionally, a $(14\beta,17\alpha)$ -3-methoxy-17-($CHR_{13}OH$)estra-1,3,5(10)-triene can be oxidized as described above to obtain a 20-ketone which can then be reacted with an (organometallic) compound of formula $R_{14}M$, R_{14} having the previously given meaning except for hydrogen, any functional groups present in R_{14} being suitably protected, and M having the previously given meaning. In that case Birch reduction, hydrolysis and removal of any protecting groups still present will provide $(14\beta,17\alpha)$ -17-($CR_{13}R_{14}OH$)estr-4-en-3-one derivatives of the invention 20 wherein R_{13} and R_{14} have the previously given meaning except for hydrogen. This procedure can also be used for the preparation of compounds of the invention in which R_{13} and R_{14} together with the carbon atom at which they are placed form a (C_{3-6})cycloalkyl ring or a (C_5-C_6)cycloalkenyl ring.

25 Optionally, the 20-ketone can be reduced by reaction with LiAlH₄, NaBH₄ or other reducing agents. In that case, $(14\beta,17\alpha)$ -17-($CHR_{13}OH$)estr-4-en-3-one derivatives are obtained of inverted stereochemistry at C-20.

30 Optionally, a $(14\beta,17\alpha)$ -3-methoxyestra-2,5(10)-diene-17-methanol derivative, *i.e.* the product obtained after the Birch reduction, can be oxidized as described above to the corresponding 17-carboxaldehyde. Reaction with a compound of formula $R_{13}M$ as described above and hydrolysis affords the $(14\beta,17\alpha)$ -17-($CHR_{13}OH$)estr-4-en-3-one derivatives of the invention as already described above. This reaction sequence allows the introduction of substituents R_{13} , and analogously, R_{14} , which would not survive a Birch reduction. Optionally, the $(14\beta,17\alpha)$ -3-

methoxyestra-2,5(10)-diene-17-methanol derivative might also be converted to a more stable system, e.g. a (14 β ,17 α)-3,3-dimethoxyestr-5(10)-ene-17-methanol derivative or a (14 β ,17 α)-17-(hydroxymethyl)estr-4-en-3-one cyclic 1,2-ethanediyl (dithio)acetal derivative, prior to oxidation and reaction with R₁₃M, and so on.

- 5 Wittig reaction of a (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative with e.g. ethyltriphenylphosphonium bromide leads predominantly to the (17Z)-ethylidene derivative which on hydroboration gives the (14 β ,17 α ,20R)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol derivative. Birch reduction and hydrolysis then results in (14 β ,17 α ,20R)-20-hydroxy-19-norpregn-4-en-3-one derivatives of the invention (R₁₃ = CH₃). On the other hand, Wittig-
10 Horner reaction with e.g. triethyl phosphonoacetate results in a ethyl (14 β ,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate, which can be converted, by methods known in the art, to a (14 β ,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene, which on hydroboration results in a (14 β ,17 α ,20S)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol derivative. Optionally, the ethyl (14 β ,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate can
15 be subjected to homologation, by using methods known in the art, prior to hydroboration to the 20-hydroxy compound, which provides an additional method to obtain a (14 β ,17 α ,20S)-17-(CHR₁₃OH)estr-4-en-3-one derivative of the invention in which R₁₃ has the previously given meaning except for hydrogen. Techniques for homologation are known in the art [Mathieu, J. et al: *Formation of C-C Bonds*, Vol. I-III, Georg Thieme Publishers, Stuttgart, 1973].
20 Compounds of formula I with substituents at C-3, C-4, C-6, C-7, C-10, C-11, C-13, C-14, C-15, C-16 and C-17 other than those described under the definition of formula II, or compounds without double bonds in the steroid nucleus or with double bonds other than a Δ^4 double bond, can be prepared as follows.
25 Compounds of the invention in which R₁ is (H,H), (H,OR), NOR, and R is H, (C₁₋₆) alkyl, or (C₁₋₆) acyl can be prepared, using standard methods, from compounds of formula I in which R₁ is oxo. Compounds in which R₂ is (C₁₋₆) alkyl or halogen are obtained, using standard methods, from compounds of formula I in which R₂ is hydrogen.
30 Compounds in which R₃ is (C₂₋₆) alkenyl or (C₂₋₆) alkynyl are obtained, using standard methods, from compounds of formula I in which R₃ is hydrogen.

Compounds in which R₅ has the meaning described above except for hydrogen or (C₁₋₆) alkyl can be prepared from e.g. (7 α ,17 β)-7-ethenyl-17-hydroxyestr-4-en-3-one which can be prepared by copper(I)-catalyzed 1,6-addition of vinyllithium or a vinylmagnesium compound to e.g. (17 β)-17-(acetoxy)estra-4,6-diene-3-one [Syntex, DE 1143199 (1963)]. Conversion to

- 5 (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-one and construction of the functionalized and/or unsaturated side-chain at C-7 from 7-ethenyl are carried out using standard methods. Inversion of the stereochemistry at C-14 and construction of the side-chain at C-17 are carried out as described above. The precise sequence of reaction steps needed for the inversion at C-14 and for the construction of the two side-chains, including the Birch reduction and the
10 hydrolysis of the resulting estra-2,5(10)-diene, is dictated by methods common in synthetic strategy.

Compounds in which R₅ is methyl can be prepared from e.g. (3 β)-3-(acetoxy)androsta-5,14-dien-17-one [Andre, A.F.St. *et al*, J. Am. Chem. Soc. 74, 5506 (1952)].

- Compounds in which R₆ has the previously given meaning except for hydrogen or (C₁₋₆) alkyl
15 can be obtained from e.g. (11 α)-11-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [Collins, D.J. *et al*, Aust. J. Chem. 36, 339 (1983)], (11 β)-11-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [Choe, Y.S. *et al*, J. Med. Chem. 38, 816 (1995)], (11 β)-11-(hydroxymethyl)-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [van den Broek, A.J. *et al*, Steroids 30, 481 (1977)], or 3-methoxyestra-1,3,5(10)-triene-11,17-dione cyclic 17-(1,2-ethanediyl acetal) [van den Broek, A.J. *et al*, Recl. Trav. Chim. Pays-Bas 94, 35 (1975)]. The precise sequence of reaction steps
20 needed for the construction of 11-substituted compounds of the invention is again dictated by methods common in synthetic strategy.

- Compounds in which R₈ is ethyl can be prepared from e.g. 13-ethylgon-4-ene-3,17-dione
25 [Brito, M. *et al*, Synth. Comm. 26, 623 (1996)].

- 14 β -Substituted compounds can be obtained by a slight modification of a method described by Bull which enables the conversion of a (17 β)-3-methoxyestra-1,3,5(10),14-tetraen-17-ol derivative to 14-substituted (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one compounds [Bull, J.R. *et al*, J. Chem. Soc., Perkin Trans. I, 37 (1987)]. The latter can be converted to the
30 compounds of the invention by methods described above.

15-Substituted compounds can be obtained as follows. Conjugated addition of an (organometallic) compound of formula R₁₀M wherein R₁₀ has the previously given meaning,

any functional groups present in R₁₀ being suitably protected, and M having the previously given meaning, to a (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative provides a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative, substituted at C-15, which can then be converted as described above to a (14β,17α)-17-(hydroxymethyl)estr-4-en-3-one derivative of the invention, substituted at C-15.

16-Substituted compounds can be obtained via alkylation at C-16 of a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative, usually resulting in the predominant formation of the 16β-isomer. Optionally, the stereochemistry at C-16 can be inverted by deprotonation followed by hydrolysis.

10 15,16-Methylene derivatives can be obtained from a (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one by reaction with trimethyl sulfoxonium iodide/base to produce a (14β,15β,16β)-3-methoxy-15,16-methyleneestra-1,3,5(10)-trien-17-one which is processed as described above.

15 17β-Substituted compounds of formula I can be obtained via alkylation of a alkyl (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-carboxylate.

Compounds of the invention in which R₁₅ is SO₃H, (C₁₋₆) alkyl, (C₁₋₁₅) acyl are obtained, by using methods known in the art, from compounds of formula I in which R₁₅ is hydrogen.

20 Compounds of the invention without unsaturations in the steroid nucleus are produced from Δ⁴ compounds wherein R₁ is oxo.

Compounds of the invention having a Δ⁵⁽¹⁰⁾ double bond, or a Δ^{4,9} diene system are produced from the Δ^{2,5(10)} dienes obtained after the Birch reduction.

Compounds having a Δ¹¹ double bond can be prepared from e.g. estra-4,11-diene-3,17-dione [Broess, A.I.A. et al, Steroids 57, 514 (1992)].

25 Compounds of the invention having a Δ¹⁵ double bond can be prepared from a (14β)-3-methoxyestra-1,3,5(10),16-tetraene-17-methanol derivative by the sequence: protection of the hydroxy group, e.g. as a *tert*-butyldimethylsilyl ether; hydroboration of the Δ¹⁶ double bond to produce a (14β,16β,17α)-17-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxyestra-1,3,5(10)-trien-16-ol, oxidation to the corresponding 16-ketone, conversion of 16-oxo to a Δ¹⁵ double bond, and finally, Birch reduction/hydrolysis.

The invention will be further explained hereinafter with reference to the following Examples.

*I) Unsubstituted compounds***Example 1**5 (14 β ,17 α)-17-(Hydroxymethyl)estr-4-en-3-one.

i) - Lithium amide (6.6 g) was added to a suspension of methyltriphenylphosphonium bromide (113 g) in dry toluene (300 ml) and dry dimethyl sulfoxide (24 ml). The reaction mixture was heated to 65 °C for 30 min. After cooling to 35-40 °C, a solution of (14 β)-3-methoxyestra-1,3,5(10)-trien-17-one [Johnson, W.S. *et al*, J. Am. Chem. Soc. **79**, 2005 (1957); 30 g] in dry toluene (225 ml) was added and the mixture was heated at 60 °C for 22 h. Then it was cooled and poured into water. The product was extracted into ethyl acetate; the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. In order to achieve complete conversion of starting material, the procedure was repeated. The triphenylphosphine oxide was removed by addition of diethyl ether and filtration. Column chromatography of the crude product afforded (14 β)-3-methoxy-17-methyleneestra-1,3,5(10)-triene (26 g).

ii) - A solution of borane-dimethyl sulfide complex (26.6 ml) in dry tetrahydrofuran (105 ml) was cooled to 0 °C. A solution of 1,5-cyclooctadiene (33 ml) in dry tetrahydrofuran (32 ml) was added dropwise in 45 min. while maintaining the temperature below 10 °C. The mixture was heated under reflux for 1 h and then cooled to 13 °C. A solution of the product obtained in the previous step (25 g) in dry tetrahydrofuran (100 ml) was added in 10 min. and the reaction mixture was heated under reflux for 2.5 h and then stirred at room temperature overnight. An aqueous solution of sodium hydroxide (3 M, 120 ml) was added in 30 min., followed by an aqueous solution of hydrogen peroxide (30 %, 120 ml) in 1 h ($T \leq 50$ °C). After 2 h stirring the reaction mixture was poured into an aqueous solution of sodium sulfite (10 %, 1.75 l) and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Trituration (ethanol/water 1:1) afforded (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-methanol (23.6 g).

iii) - The alcohol obtained in the previous step (2.0 g) in dry tetrahydrofuran (35 ml) was added to a solution of lithium (0.86 g) in liquid ammonia (52 ml), cooled between -50 °C and -60 °C. After 1 h stirring at -50 °C and 1 h at -40 °C, dry ethanol was added and the ammonia was allowed to evaporate. Water was added and the product was extracted into ethyl acetate. The

combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($14\beta,17\alpha$)-3-methoxyestra-2,5(10)-diene-17-methanol (2.13 g). The product was used in the following step without further purification.

iv) - A solution of the diene obtained in the previous step (0.30 g) in acetone (12 ml)

5 treated with hydrochloric acid (2-6 M, 0.6 ml). After 0.1-2 h stirring at room temperature, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, or with an aqueous solution of sodium hydroxide (1 M) followed by addition of a saturated aqueous solution of sodium hydrogencarbonate. Optionally, the acetone was evaporated under reduced pressure. The product was extracted into ethyl acetate; the
10 combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography and crystallization afforded ($14\beta,17\alpha$)-17-(hydroxymethyl)estr-4-en-3-one (0.21 g), m.p. 115-118 °C.

15 **Example 2**

($14\beta,17\alpha$)-17-(Hydroxymethyl)estr-5(10)-en-3-one.

A solution of ($14\beta,17\alpha$)-3-methoxyestra-2,5(10)-diene-17-methanol (Example 1, step iii; 0.30 g) in a mixture of methanol (3 ml) and tetrahydrofuran (2.1 ml) was treated with a solution of oxalic acid (0.105 g) in water (1.8 ml). After 1.5 h stirring at room temperature, the reaction

20 mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded ($14\beta,17\alpha$)-17-(hydroxymethyl)estr-5(10)-en-3-one (0.20 g), ^1H NMR δ 3.77 (m, 1H), 3.52 (t, 1H, J = 9.0 Hz), 2.74 (m, 2H), 1.09 (s, 3H).

25

Example 3

($14\beta,17\alpha$)-17-(Hydroxymethyl)estra-4,9-dien-3-one.

Phenyltrimethylammonium tribromide (2.28 g) was added in small portions and in 10 min. to a

30 solution of ($14\beta,17\alpha$)-17-(hydroxymethyl)estr-5(10)-en-3-one (Example 2; 1.75 g) in dry

pyridine (47 ml). After 1.5 h stirring at room temperature the mixture was poured into ice-water and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate, water, a saturated aqueous

solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography provided (14 β ,17 α)-17-(hydroxymethyl)estra-4,9-dien-3-one (0.36 g), $[\alpha]_D^{20} = -241^\circ$ (c = 1, dioxane).

5 2) *7-Substituted compounds*

Example 4

(7 α ,14 β ,17 α)-17-(Hydroxymethyl)-7-methylestr-4-en-3-one.

- i) - A mixture of $(7\alpha,17\beta)$ -3-methoxy-7-methylestra-1,3,5(10),14-tetraen-17-ol [Segaloff, A. et al, Steroids 22, 99 (1973); 86.2 g] and palladium on activated carbon (5 %; 34.5 g) in ethanol (578 ml) and dichloromethane (414 ml) was stirred under hydrogen (3 bar) at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, to give $(7\alpha,14\beta,17\beta)$ -3-methoxy-7-methylestra-1,3,5(10)-trien-17-ol (83.0 g). The product was used in the following step without further purification.
- ii) - A solution of the product obtained in the previous step (37.4 g) in acetone (1880 ml) was cooled to 0 °C. Jones reagent (8 M, 37.4 ml) was added dropwise while keeping the temperature below 10 °C. The reaction mixture was stirred for 30 min. 2-Propanol (21 ml) was added and after 10 min. stirring the mixture was filtered over dicalite. The filtrate was partially concentrated under reduced pressure and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate, a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure, to give $(7\alpha,14\beta)$ -3-methoxy-7-methylestra-1,3,5(10)-trien-17-one (35.85 g). The product was used in the following step without further purification.
- iii) - A mixture of methyltriphenylphosphonium bromide (21.8 g), potassium *tert*-butoxide (5.7 g) and dry toluene (218 ml) was heated under reflux for 1 h. A solution of the ketone obtained in the previous step (6.07 g) in dry toluene (50 ml) was added dropwise and heating was continued for another 1 h. After cooling, the reaction mixture was poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography of the crude product afforded $(7\alpha,14\beta)$ -3-methoxy-7-methyl-17-methyleneestra-1,3,5(10)-triene (5.85 g).
- iv) - A solution of borane-dimethyl sulfide complex (5.94 ml) in dry tetrahydrofuran (27 ml) was cooled to 0 °C. A solution of 1,5-cyclooctadiene (7.36 ml) in dry tetrahydrofuran (7 ml)

was added dropwise while maintaining the temperature below 10 °C. The mixture was heated under reflux for 1 h and then cooled to room temperature. A solution of the product obtained in the previous step (5.85 g) in dry tetrahydrofuran (70 ml) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, and an aqueous solution of sodium hydroxide (2 M, 14.75 ml) was added carefully ($T \leq 15$ °C), followed by an aqueous solution of hydrogen peroxide (30 %, 11.8 ml). After 2 h stirring the reaction mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with an aqueous solution of sodium thiosulfate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded $(7\alpha,14\beta,17\alpha)$ -3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (1.60 g).

v) - The alcohol obtained in the previous step (1.06 g) in dry tetrahydrofuran (15 ml) was added to a refluxing solution of lithium (1.35 g) in liquid ammonia (64 ml). After 4 h stirring, *tert*-butanol was added and stirring was continued for 30 min. Ethanol was added and the ammonia was allowed to evaporate. The mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give $(7\alpha,14\beta,17\alpha)$ -3-methoxy-7-methylestra-2,5(10)-diene-17-methanol (0.79 g). The product was used in the following step without further purification.

vi) - Following a procedure analogous to that described under iv of Example 1, the diene obtained in the previous step (0.79 g) was converted to $(7\alpha,14\beta,17\alpha)$ -17-(hydroxymethyl)-7-methylestr-4-en-3-one (0.36 g), m.p. 157-159 °C.

Example 5

25 $(7\alpha,14\beta,17\alpha)$ -17-(Hydroxymethyl)-7-methylestra-4,15-dien-3-one.

i) - *m*-Chloroperbenzoic acid (70-75 %, 14.57 g) was added to a solution of $(7\alpha,14\beta)$ -3-methoxy-7-methyl-17-methyleneestra-1,3,5(10)-triene (Example 4, step iii; 16.05 g) in diethyl ether (642 ml), containing solid sodium hydrogencarbonate (45.5 g). The reaction mixture was stirred at room temperature for 6 h. Additional *m*-chloroperbenzoic acid (14.57 g) was added and stirring was continued overnight. The reaction was poured into a saturated aqueous solution of sodium thiosulfate and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under

reduced pressure, to give ($7\alpha,14\beta,17\beta$)-3-methoxy-7-methylspiroestra-1,3,5(10)-triene[17,2']oxirane (16.88 g). The product was used in the next step without further purification.

ii) - A solution of the product obtained in the previous step (16.88 g) in dry 2-propanol (844

5 ml), containing aluminium isopropoxide (46.88 g), was heated under reflux for 3 h. After cooling, a saturated aqueous solution of potassium sodium tartrate tetrahydrate was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded ($7\alpha,14\beta$)-3-methoxy-7-methylestra-1,3,5(10),16-tetraene-17-methanol (8.68 g).

10
iii) - A solution of the product obtained in the previous step (1.50 g) and imidazole (3.07 g) in dry dichloromethane (9.4 ml) was treated with *t*-butyldimethylsilyl chloride (1.38 g). After 2 h stirring at room temperature the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into ethyl acetate; the combined 15 organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta$)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methylestra-1,3,5(10),16-tetraene (2.54 g). The product was used in the next step without further purification.

iv) - Following a procedure analogous to that described under iv of Example 4, the product 20 obtained in the previous step (1.57 g) was converted to ($7\alpha,14\beta,16\beta,17\alpha$)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methylestra-1,3,5(10)-trien-16-ol (1.98 g).

v) - Tetrapropylammonium perruthenate (0.080 g) was added to a solution of the product obtained in the previous step (1.69 g) and 4-methylmorpholine *N*-oxide (1.33 g) in acetone (31 25 ml). After 1.5 h stirring at room temperature the reaction mixture was filtered over dicalite and silica. The filtrate was concentrated under reduced pressure. Column chromatography of the crude product gave ($7\alpha,14\beta,17\alpha$)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methylestra-1,3,5(10)-trien-16-one (1.02 g).

vi) - A solution of 1,1,1,3,3,3-hexamethyldisilazane (0.98 ml) in dry tetrahydrofuran (2.3 ml),

30 cooled to 0 °C, was treated with *n*-butyllithium (1.6 M solution in hexane, 2.87 ml). After 5 min. stirring, a solution of the product obtained in the previous step (1.02 g) in dry tetrahydrofuran (2.3 ml) was added and stirring was continued for 1 h. *N*-

Phenyltrifluoromethanesulfonimide (2.5 g) was added and the reaction mixture was stirred for another 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

5 Column chromatography afforded $(7\alpha,14\beta,17\alpha)$ -17-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methyl-16-
[[[trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),15-tetraene (0.69 g).

vii) - A solution of the product obtained in the previous step (0.69 g) in dry dimethyl formamide (7.8 ml) was treated with palladium(II) acetate (37.9 mg), triphenylphosphine (89.7 mg), formic acid (0.322 ml), and diisopropylethylamine (3.10 ml) and the mixture was heated at 60 °C for 30 min. The reaction mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded $(7\alpha,14\beta,17\alpha)$ -17-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methylestra-1,3,5(10),15-tetraene (0.48 g).

viii) - Lithium granulate (0.80 g) was added in portions to a refluxing solution of the product obtained in the previous step (0.48 g) in dry tetrahydrofuran (40 ml) and liquid ammonia (90 ml) and the reaction mixture was stirred for 3 h. Dry *tert*-butanol (2 ml) was added dropwise and stirring was continued for 30 min. Ethanol was added and the ammonia was allowed to evaporate. Water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give $(7\alpha,14\beta,17\alpha)$ -17-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methoxy-7-methylestra-2,5(10),15-triene (0.51 g). The product was used in the following step without further purification.

ix) - Following a procedure analogous to that described under iv of Example 1, the diene obtained in the previous step (0.51 g) was converted to $(7\alpha,14\beta,17\alpha)$ -17-(hydroxymethyl)-7-methylestra-4,15-dien-3-one, ¹H NMR δ 6.10 (dm, 1H, J = 6.7 Hz), 5.83 (m, 1H), 5.71 (dm, 1H, J = 6.7 Hz), 3.75 (m, 1H), 3.65 (m, 1H), 1.26 (s, 3H), 1.11 (m, 2H), 0.97 (t, 3H, J = 7.1 Hz).

Example 6

(7 α ,14 β ,17 α)-17-(Hydroxymethyl)-7,14-dimethylestr-4-en-3-one.

- i) - Following a procedure analogous to that described under iii of Example 5, (7 α ,17 β)-3-methoxy-7-methylestra-1,3,5(10),14-tetraen-17-ol (Example 4, step i; 15.0 g) was converted to (7 α ,17 β)-17-[[$(1,1$ -dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10),14-tetraene (21.9 g). The product was used in the next step without further purification.
- ii) - A solution of the product obtained in the previous step (19.33 g) in dry tetrahydrofuran (20 ml) was treated with borane-methylsulfide complex (27 ml) and the reaction mixture was stirred at room temperature for 2 h. Then it was diluted with tetrahydrofuran (350 ml) and cooled to 0 °C. An aqueous solution of sodium hydroxide (2 M, 125 ml) was added carefully, followed by aqueous hydrogen peroxide (30 %, 80 ml). The mixture was stirred at room temperature overnight. Then it was poured into brine and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,15 α ,17 β)-17-[[$(1,1$ -dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-15-ol (7.64 g) and (7 α ,14 β ,15 β ,17 β)-17-[[$(1,1$ -dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-15-ol (2.43 g).
- iii) - Following a procedure analogous to that described under v of Example 5, the 15 α -hydroxy compound obtained in the previous step (7.42 g) was converted to (7 α ,17 β)-17-[[$(1,1$ -dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-15-one (8.48 g).
- iiib) - Following a procedure analogous to that described under v of Example 5, the 15 β -hydroxy compound obtained in step ii (2.23 g) was converted to (7 α ,14 β ,17 β)-17-[[$(1,1$ -dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-15-one (2.20 g).
- iv) - A solution of the products of step iiiia and iiib (10.68 g totally) in a mixture of dry tetrahydrofuran (68 ml) and dry *tert*-butanol (203 ml) was treated with potassium *tert*-butoxide (12.6 g) and the reaction mixture was stirred at room temperature for 1 h. Iodomethane (34 ml) was added and stirring was continued for 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7 α ,14 β)-3-methoxy-7,14-dimethylestra-

1,3,5(10),16-tetraen-15-one (7.67 g). The product was used in the following step without further purification.

v) - Aqueous hydrogen peroxide (30 %, 300 ml) was added in 30 ml aliquots, at intervals of 30 min., while maintaining the temperature between 15 °C and 20 °C, to a stirred solution of the

5 product obtained in the previous step (3.77 g) in a mixture of tetrahydrofuran (600 ml) and *tert*-butanol (600 ml), containing aqueous potassium hydroxide (20 %, 18 ml). The reaction mixture was stirred overnight (15 < T < 20 °C) and then poured into a mixture of water and brine (1:1). The product was extracted into ethyl acetate; the combined organic phases were washed with brine, a saturated aqueous solution of sodium thiosulfate, and brine, dried over 10 sodium sulfate and concentrated under reduced pressure, to give (7 α ,14 β ,16 β ,17 β)-16,17-epoxy-3-methoxy-7,14-dimethylestra-1,3,5(10)-trien-15-one (3.55 g). The product was used in the following step without further purification.

vi) - Lithium aluminium hydride (0.565 g) was added to a solution of the product obtained in the previous step (5.65 g) in dry tetrahydrofuran (113 ml), cooled to 0 °C. The reaction mixture

15 was heated under reflux for 1 h. After cooling, it was quenched with a saturated aqueous solution of sodium sulfate. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,15 β ,17 β)-3-methoxy-7,14-dimethylestra-1,3,5(10)-triene-15,17-diol (2.27 g).

vii) - Benzoyl chloride (0.60 ml) was added to a solution of the product obtained in the

20 previous step (1.70 g) in dry pyridine (20.6 ml), cooled to 0 °C. The reaction mixture was stirred at 0 °C for 4 h; additional portions of benzoyl chloride (0.15 ml) were added after 2 and 3 h, respectively. Water was added and stirring was continued at room temperature for 1 h. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and the product was extracted into ethyl acetate. The combined organic phases were washed 25 with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,15 β ,17 β)-3-methoxy-7,14-dimethylestra-1,3,5(10)-triene-15,17-diol 17-benzoate (1.53 g).

viii) - Pyridinium *p*-toluenesulfonate (0.30 g) was added to a solution of the product obtained in the previous step (1.31 g) in a mixture of dry dichloromethane (18 ml) and ethyl vinyl ether

30 (6 ml). After 2 h stirring at room temperature, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into diethyl ether; the combined organic phases were washed with brine, dried over sodium sulfate and

concentrated under reduced pressure, to give ($7\alpha,14\beta,15\beta,17\beta$)-15-[(1-ethoxyethyl)oxy]-3-methoxy-7,14-dimethylestra-1,3,5(10)-trien-17-ol benzoate (1.64 g). The product was used in the following step without further purification.

ix) - A solution of the product obtained in the previous step (1.64 g) in dry tetrahydrofuran (70 ml) was added dropwise to a suspension of lithium aluminium hydride (0.50 g) in tetrahydrofuran (30 ml). After stirring of the mixture for 30 min., the reaction was quenched by addition of a saturated aqueous solution of sodium sulfate. The reaction mixture was filtered over dicalite and the filtrate was concentrated under reduced pressure, to give ($7\alpha,14\beta,15\beta,17\beta$)-15-[(1-ethoxyethyl)oxy]-3-methoxy-7,14-dimethylestra-1,3,5(10)-trien-17-ol (1.50 g). The product was used in the following step without further purification.

x) - Following a procedure analogous to that described under v of Example 5, the product obtained in the previous step (1.50 g) was converted to ($7\alpha,14\beta,15\beta$)-15-[(1-ethoxyethyl)oxy]-3-methoxy-7,14-dimethylestra-1,3,5(10)-trien-17-one (1.55 g).

xi) - Sodium hydride (60 % suspension in mineral oil, 0.60 g) was added to a solution of the product obtained in the previous step (1.55 g) in a mixture of dry tetrahydrofuran (15 ml) and dry 2-propanol (30 ml). After 5 min. stirring at room temperature, the mixture was poured into a saturated aqueous solution of ammonium chloride. The product was extracted into diethyl ether; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded ($7\alpha,14\beta$)-3-methoxy-7,14-dimethylestra-1,3,5(10),15-tetraen-17-one (1.01 g).

xii) - A solution of the product obtained in the previous step (0.90 g) and triethylsilane (1.8 ml) in dichloromethane (18 ml) was cooled to -40 °C. Titanium(IV) chloride (1.0 ml) was added dropwise and the reaction mixture was stirred at -30 °C for 30 min. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and the product was extracted into diethyl ether. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta$)-3-methoxy-7,14-dimethylestra-1,3,5(10)-trien-17-one (0.89 g). The product was used in the following step without further purification.

xiii) - Following a procedure analogous to that described under iii of Example 4, the product obtained in the previous step (0.68 g) was converted to ($7\alpha,14\beta$)-3-methoxy-7,14-dimethyl-17-methyleneestra-1,3,5(10)-triene (0.50 g).

xiv) - Following a procedure analogous to that described under ii, the product obtained in the previous step (0.50 g) was converted to a mixture of ($7\alpha,14\beta,17\alpha$)-3-methoxy-7,14-dimethylestra-1,3,5(10)-triene-17-methanol and ($7\alpha,14\beta,17\beta$)-3-methoxy-7,14-dimethylestra-1,3,5(10)-triene-17-methanol (0.35 g, ratio 1:1).

5 xv) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.35 g) was converted to a mixture of ($7\alpha,14\beta,17\alpha$)-3-methoxy-7,14-dimethylestra-2,5(10)-diene-17-methanol and ($7\alpha,14\beta,17\beta$)-3-methoxy-7,14-dimethylestra-2,5(10)-diene-17-methanol (0.39 g, ratio 1:1).

xvi) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.39 g) was converted to a mixture of ($7\alpha,14\beta,17\alpha$)-17-(hydroxymethyl)-7,14-dimethylestr-4-en-3-one and ($7\alpha,14\beta,17\beta$)-17-(hydroxymethyl)-7,14-dimethylestr-4-en-3-one (0.16 g, ratio 1:1), ^1H NMR δ 5.80 (m, 1H), 3.83 (dd, 0.5H, J = 10.2 and 6.0 Hz), 3.74 (dd, 0.5H, J = 10.2 and 5.6 Hz), 3.52 (m, 1H), 1.01 (s, 1.5H), 0.97 (s, 1.5H), 0.93 (s, 1.5H), 0.91 (s, 1.5H), 0.80 (d, 1.5H, J = 7.0 Hz), 0.78 (d, 1.5H, J = 7.2 Hz).

15

Example 7

($7\alpha,14\beta,15\beta,17\alpha$)-17-(Hydroxymethyl)-7,15-dimethylestr-4-en-3-one.

i) - *p*-Toluenesulfonic acid (0.248 g) was added to a solution of ($7\alpha,14\beta$)-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one (Example 4, step ii; 5.0 g) in a mixture of ethylene glycol

20 (8.0 ml) and triethyl orthoformate (14.5 ml). The reaction mixture was stirred at room temperature for 2.5 h. Water was added and stirring was continued for 1 h. The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta$)-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (6.14 g). The product was used in the following step without further purification.

25 ii) - Phenyltrimethylammonium tribromide (4.75 g) was added to a solution of the product obtained in the previous step (5.41 g) in dry tetrahydrofuran (32 ml). After 1.5 h stirring the mixture was poured into a saturated aqueous solution of sodium thiosulfate. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta,16\beta$)-16-

30

bromo-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (8.17 g).

The product was used in the following step without further purification.

iii) - A solution of the product obtained in the previous step (8.17 g) in dry dimethyl sulfoxide (32 ml) was treated with potassium *tert*-butoxide (7.10 g) and the reaction mixture was stirred

5 at room temperature for 1 h. Additional potassium *tert*-butoxide (3.50 g) was added and the reaction mixture was stirred for another 2 h. The mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7 α ,14 β)-3-methoxy-7-methylestra-1,3,5(10),15-tetraen-17-one cyclic 1,2-ethanediyl acetal (5.48 g). The product was used in the following 10 step without further purification.

iv) - A solution of the product obtained in the previous step (5.84 g) in a mixture of acetone (98 ml) and water (8.2 ml) was treated with *p*-toluenesulfonic acid (0.283 g) and the reaction mixture was stirred at room temperature for 2.5 h. Then it was poured into a saturated aqueous 15 solution of sodium hydrogencarbonate and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β)-3-methoxy-7-methylestra-1,3,5(10),15-tetraen-17-one (2.90 g).

v) - A solution of the product obtained in the previous step (2.17 g) in dry tetrahydrofuran (107 ml), containing copper(II) acetate (0.73 g), was cooled to -20 °C. Methylmagnesium chloride (3 M solution in tetrahydrofuran, 18.0 ml) was added dropwise and the reaction mixture was stirred for 1 h. Then it was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of ammonium chloride and brine, dried over sodium sulfate and 25 concentrated under reduced pressure, to give (7 α ,14 β ,15 β)-3-methoxy-7,15-dimethylestra-1,3,5(10)-trien-17-one (2.38 g). The product was used in the following step without further purification.

vi) - Following a procedure analogous to that described under iii of Example 4, the product obtained in the previous step (1.96 g) was converted to (7 α ,14 β ,15 β)-3-methoxy-7,15-30 dimethyl-17-methyleneestra-1,3,5(10)-triene (1.30 g).

vii) - Following a procedure analogous to that described under iv of Example 4, the product obtained in the previous step (1.30 g) was converted to ($7\alpha,14\beta,15\beta,17\alpha$)-3-methoxy-7,15-dimethylestra-1,3,5(10)-triene-17-methanol (0.93 g).

5 viii) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.93 g) was converted to ($7\alpha,14\beta,15\beta,17\alpha$)-3-methoxy-7,15-dimethylestra-2,5(10)-diene-17-methanol (0.93 g).

ix) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.93 g) was converted to ($7\alpha,14\beta,15\beta,17\alpha$)-17-(hydroxymethyl)-7,15-dimethylestr-4-en-3-one (0.27 g), $[\alpha]_D^{20} = +93.2^\circ$ (c = 0.56, dioxane).

10

Example 8

($7\alpha,14\beta,16\alpha,17\alpha$)-17-(Hydroxymethyl)-7,16-dimethylestr-4-en-3-one.

i) - A solution of lithium bis(trimethylsilyl)amide (55.5 mmol) in tetrahydrofuran (96 ml) was cooled to -40 °C. A solution of ($7\alpha,14\beta$)-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one

15 (Example 4, step ii; 15.0 g) in dry tetrahydrofuran (66 ml) was added dropwise and the reaction mixture was stirred for 45 min. Then, at -30 °C, iodomethane (6.3 ml) was added and stirring was continued for 1 h (-30 < T -20 °C). The mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta,16\beta$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-trien-17-one (17.33 g). The product was used in the following step without further purification.

20 ii) - A solution of lithium bis(trimethylsilyl)amide (29 mmol) in tetrahydrofuran (45 ml) was cooled to -40 °C. A solution of the product obtained in the previous step (6.0 g) in dry tetrahydrofuran (24 ml) was added dropwise and the reaction mixture was stirred for 1 h. Then it was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta,16\alpha$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-trien-17-one (6.82 g). The product was used in the next step without further purification.

25 iii) - Following a procedure analogous to that described under iii of Example 4, the product obtained in the previous step (5.14 g) was converted to a mixture of ($7\alpha,14\beta,16\alpha$)-3-methoxy-

7,16-dimethyl-17-methyleneestra-1,3,5(10)-triene and ($7\alpha,14\beta,16\beta$)-3-methoxy-7,16-dimethyl-17-methyleneestra-1,3,5(10)-triene (3.78 g, ratio 1:1).

iv) - Following a procedure analogous to that described under iv of Example 4, the product obtained in the previous step (4.56 g) was converted to ($7\alpha,14\beta,16\alpha,17\alpha$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-triene-17-methanol (2.40 g) and ($7\alpha,14\beta,16\beta,17\beta$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-triene-17-methanol (0.70 g).

v) - Following a procedure analogous to that described under v of Example 4, ($7\alpha,14\beta,16\alpha,17\alpha$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-triene-17-methanol (2.31 g) was converted to ($7\alpha,14\beta,16\alpha,17\alpha$)-3-methoxy-7,16-dimethylestra-2,5(10)-diene-17-methanol (2.41 g).

vi) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (2.41 g) was converted to ($7\alpha,14\beta,16\alpha,17\alpha$)-17-(hydroxymethyl)-7,16-dimethylestr-4-ene-3-one (0.92 g), $[\alpha]_D^{20} = +64.1^\circ$ ($c = 0.535$, dioxane).

15 Example 9

($7\alpha,14\beta,16\beta,17\alpha$)-17-(Hydroxymethyl)-7,16-dimethylestr-4-en-3-one.

i) - *m*-Chloroperbenzoic acid (70-75 %, 1.7 g) was added to a solution of a mixture of ($7\alpha,14\beta,16\alpha$)-3-methoxy-7,16-dimethyl-17-methyleneestra-1,3,5(10)-triene and ($7\alpha,14\beta,16\beta$)-3-methoxy-7,16-dimethyl-17-methyleneestra-1,3,5(10)-triene (Example 8, step iii; 5.58 g, ratio 1:1) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 6 h; additional portions of *m*-chloroperbenzoic acid (1.7 g and 0.64 g) were added after 1.5 h and 2.5 h, respectively. The reaction was poured into a saturated aqueous solution of sodium sulfite and the mixture was stirred at room temperature for 1 h. The product was extracted into dichloromethane; the combined organic phases were washed with an aqueous solution of

20 sodium hydroxide (10 %) and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded a mixture of ($7\alpha,14\beta,16\beta,17\alpha$)-3-methoxy-7,16-dimethylspiroestra-1,3,5(10)-triene[17,2']oxirane and ($7\alpha,14\beta,16\beta,17\beta$)-3-methoxy-7,16-dimethylspiroestra-1,3,5(10)-triene[17,2']oxirane (2.31 g, ratio 1:1).

ii) - A solution of the product obtained in the previous step (1.45 g) in 1,4-dioxane (44 ml) was treated with an aqueous solution of perchloric acid (70 %, 0.29 ml). The reaction mixture was stirred at room temperature for 45 min. and then poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into ethyl acetate; the combined organic

phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta,16\beta,17\alpha$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-triene-17-carboxaldehyde (1.42 g). The product was used in the following step without further purification.

- 5 iii) - Following a procedure analogous to that described under ix of Example 6, the product obtained in the previous step (1.42 g) was converted to ($7\alpha,14\beta,16\beta,17\alpha$)-3-methoxy-7,16-dimethylestra-1,3,5(10)-triene-17-methanol (0.52 g).
- iv) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.80 g) was converted to ($7\alpha,14\beta,16\beta,17\alpha$)-3-methoxy-7,16-dimethylestra-2,5(10)-diene-17-methanol (0.64 g).
- 10 v) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.64 g) was converted to ($7\alpha,14\beta,16\beta,17\alpha$)-17-(hydroxymethyl)-7,16-dimethylestr-4-en-3-one (0.22 g), $[\alpha]_D^{20} = +101.0^\circ$ ($c = 0.49$, dioxane).

15 **Example 10**

($7\alpha,14\beta,15\beta,16\beta,17\alpha$)-17-(Hydroxymethyl)-7-methyl-15,16-methyleneestr-4-en-3-one.

- i) - Sodium hydride (60 % suspension in mineral oil, 1.15 g) was added to a suspension of trimethylsulfoxonium iodide (5.57 g) in dry dimethyl sulfoxide (115 ml) and the mixture was stirred at room temperature for 20 min. ($7\alpha,14\beta$)-3-Methoxy-7-methylestra-1,3,5(10),15-tetraen-17-one (Example 7, step iv; 1.92 g) was added and stirring was continued for 1.5 h. The reaction mixture was poured into ice-water and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,14\beta,15\beta,16\beta$)-3-methoxy-7-methyl-15,16-methyleneestra-1,3,5(10)-trien-17-one (2.65 g). The product was used in the following step without further purification.
- 20 ii) - Potassium *tert*-butoxide (2.56 g) was added in portions to a solution of the product obtained in the previous step (2.25 g) in dry dimethylformamide (58 ml), containing trimethylsulfonium iodide (3.2 g). The reaction mixture was stirred at room temperature for 1.5 h and then poured into an aqueous solution of ammonium chloride. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to obtain ($7\alpha,14\beta,15\beta,16\beta,17\alpha$)-3-
- 25
- 30

methoxy-7-methyl-15,16-methylenespiroestra-1,3,5(10)-triene[17,2']oxirane (2.31 g). The product was used in the following step without further purification.

iii) - Following a procedure analogous to that described under ii of Example 9, the product obtained in the previous step (2.31 g) was converted to (7 α ,14 β ,15 β ,16 β ,17 α)-3-methoxy-7-

5 methyl-15,16-methylenestra-1,3,5(10)-triene-17-carboxaldehyde (2.27 g).

iv) - Following a procedure analogous to that described under ix of Example 6, the product obtained in the previous step (0.70 g) was converted to (7 α ,14 β ,15 β ,16 β ,17 α)-3-methoxy-7-methyl-15,16-methylenestra-1,3,5(10)-triene-17-methanol (0.38 g).

v) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.38 g) was converted to (7 α ,14 β ,15 β ,16 β ,17 α)-3-methoxy-7-methyl-15,16-methylenestra-2,5(10)-diene-17-methanol (0.36 g).

vi) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.36 g) was converted to (7 α ,14 β ,15 β ,16 β ,17 α)-17-(hydroxymethyl)-7-methyl-15,16-methylenestr-4-en-3-one (0.21 g), $[\alpha]_D^{20} = +67.6^\circ$ ($c = 0.58$,

15 dioxane).

Example 11

(7 α ,14 β ,17 α)-17-(Hydroxymethyl)-7,17-dimethylestr-4-en-3-one.

i) - Following a procedure analogous to that described under step ii of Example 4, using the double amount of Jones reagent, (7 α ,14 β ,17 α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (Example 4, step iv; 2.0 g) was converted to (7 α ,14 β ,17 α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-carboxylic acid (2.09 g).

ii) - A solution of the product obtained in the previous step (2.09 g) and dry pyridine (0.77 ml) in dry toluene (50 ml), cooled to 5-10 °C, was treated with a solution of oxalyl chloride (0.77

25 ml) in dry toluene (1 ml). The reaction mixture was stirred at room temperature for 2 h. After cooling to 0-5 °C, dry methanol (2.6 ml) was added dropwise and stirring was continued at 10-15 °C for 1.5 h. The mixture was poured into ice-water and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give methyl (7 α ,14 β ,17 α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-carboxylate (2.30 g). The product was used in the following step without further purification.

- iii) - A solution of diisopropylamine (2.38 ml) in dry tetrahydrofuran (5 ml), cooled to -70 °C, was treated with *n*-butyllithium (1.6 M solution in hexane, 8.86 ml). The mixture was warmed up to 0 °C and then cooled to -70 °C. A solution of the product obtained in the previous step (1.94 g) in dry tetrahydrofuran (4 ml) was added and the temperature was allowed to raise to 0 5 °C. After cooling to -70 °C, a solution of iodomethane (1.06 ml) in dry tetrahydrofuran (2 ml) was added dropwise. The cooling bath was removed, the reaction mixture was stirred for 2 h and then poured into a saturated aqueous solution of ammonium chloride. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give methyl (7 α ,14 β ,17 10 α)-3-methoxy-7,17-dimethylestra-1,3,5(10)-triene-17-carboxylate (2.10 g). The product was used in the following step without further purification.
- iv) - Following a procedure analogous to that described under step ix of Example 6, the product obtained in the previous step (2.1 g) was converted to (7 α ,14 β ,17 α)-3-methoxy-7,17-dimethylestra-1,3,5(10)-triene-17-methanol (1.81 g).
- v) - Lithium granulate (1.16 g) was added in portions to a refluxing solution of the alcohol obtained in the previous step (1.81 g) in dry tetrahydrofuran (40 ml) and liquid ammonia (120 ml). After 30 min. stirring, dry ethanol (10 ml) was added dropwise. Stirring was continued for 30 min.; solid ammonium chloride (3.5 g) was added and the ammonia was allowed to evaporate. Water was added and the product was extracted into ethyl acetate. The combined 20 organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7 α ,14 β ,17 α)-3-methoxy-7,17-dimethylestra-2,5(10)-diene-17-methanol (1.73 g). The product was used in the following step without further purification.
- vi) - Following a procedure analogous to that described under step iv of Example 1, the product obtained in the previous step (1.73 g) was converted to (7 α ,14 β ,17 α)-17-(hydroxymethyl)-25 25 7,17-dimethylestr-4-en-3-one (0.82 g), m.p. 190-192 °C.

Example 12

(7 α ,14 β ,17 α)-17-Fluoro-17-(hydroxymethyl)-7-methylestr-4-en-3-one.

- i) - Following a procedure analogous to that described under i of Example 9, (7 α ,14 β)-3-methoxy-7-methyl-17-methyleneestra-1,3,5(10)-triene (Example 4, step iii; 2.96 g) was converted to (7 α ,14 β ,17 β)-3-methoxy-7-methylspiroestra-1,3,5(10)-triene[17,2']oxirane (2.94 g).

- ii) - A solution of the epoxide obtained in the previous step (0.31 g) in dry dichloromethane (10 ml) was cooled to 0 °C. Hydrogen fluoride-pyridine (70 % HF, 0.1 ml) was added and the reaction mixture was stirred for 3 h. Another portion of hydrogen fluoride-pyridine (0.1 ml) was added and the reaction mixture was stirred for another 3 h. The mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into dichloromethane; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,17 α)-17-fluoro-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol, contaminated with (7 α ,14 β)-3-methoxy-7-methylestra-1,3,5(10),16-tetraene-17-methanol (0.12 g).
- iii) - A solution of the mixture obtained in the previous step (0.12 g), dry pyridine (0.50 ml) and acetic anhydride (0.30 ml) in dry tetrahydrofuran (5 ml) was stirred at room temperature for 72 h. The reaction mixture was poured into ice-water, and after 1 h stirring, the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,17 α)-17-[(acetyloxy)methyl]-17-fluoro-3-methoxy-7-methylestra-1,3,5(10)-triene (0.090 g).
- iv) - Following a procedure analogous to that described under v of Example 11, the product obtained in the previous step (0.080 g) was converted to (7 α ,14 β ,17 α)-17-fluoro-3-methoxy-7-methylestra-2,5(10)-diene-17-methanol (0.080 g).
- v) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.080 g) was converted to (7 α ,14 β ,17 α)-17-fluoro-17-(hydroxymethyl)-7-methylestr-4-en-3-one (0.026 g). M.p. 145-146 °C.

25 **Example 13**

(7 α ,14 β ,17 β)-17-Hydroxy-17-(hydroxymethyl)-7-methylestr-4-en-3-one.

- i) - A solution of (7 α ,14 β ,17 β)-3-methoxy-7-methylspirostra-1,3,5(10)-triene[17,2']oxirane (Example 12, step i; 0.91 g) in *tert*-butanol (70 ml), containing potassium hydroxide (4.5 g), was refluxed overnight. The reaction mixture was poured into water and neutralized with aqueous hydrochloric acid (2 M). The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under

reduced pressure. Column chromatography afforded ($7\alpha,14\beta,17\beta$)-17-hydroxy-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (0.21 g).

ii) - Following a procedure analogous to that described under iii of Example 1, the product obtained in the previous step (0.21 g) was converted to ($7\alpha,14\beta,17\beta$)-17-hydroxy-3-methoxy-

5 7-methylestra-2,5(10)-diene-17-methanol (0.21 g).

iii) - Following a procedure analogous to that described under iv of Example 1, using methanol as solvent, the product obtained in the previous step (0.13 g) was converted to ($7\alpha,14\beta,17\beta$)-17-hydroxy-17-(hydroxymethyl)-7-methylestr-4-en-3-one (0.093 g), m.p. 163-167 °C.

10 **Example 14**

($7\alpha,14\beta,17\alpha$)-7-Ethyl-17-(hydroxymethyl)estr-4-en-3-one.

i) - Vinylmagnesium chloride in tetrahydrofuran (2 M, 159.2 ml) was added dropwise to a mixture of (17β)-17-(acetoxy)estra-4,6-diene-3-one [Syntex, DE 1143199 (1963); 50.0 g],

15 copper(I) bromide-dimethyl sulfide complex (3.18 g), lithium bromide (1.38 g), and lithium thiophenoxyde (16 ml of a 1 M solution in tetrahydrofuran), in dry tetrahydrofuran (167 ml),

cooled to -15 °C. After 30 min. stirring a saturated aqueous solution of ammonium chloride was added and the product extracted into ethyl acetate. The combined organic phases were concentrated under reduced pressure whereafter the residue was dissolved in acetone (1000 ml) and treated with hydrochloric acid (4 M, 100 ml). After 30 min. stirring at room temperature,

20 the mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. Part of the acetone was removed under reduced pressure and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($7\alpha,17\beta$)-17-(acetoxy)-7-ethenylestr-4-en-3-one (59.4 g). The product was used in the following step without further purification.

25 ii) - Powdered potassium hydroxide (26.7 g) was added to a solution of the product obtained in the previous step (59.4 g) in a mixture of tetrahydrofuran (833 ml), methanol (738 ml), and water (238 ml). The reaction mixture was stirred at room temperature for 45 min. and then neutralized with concentrated hydrochloric acid (20 ml). The tetrahydrofuran and the methanol were removed under reduced pressure and the product was extracted into ethyl acetate. The

30 combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded ($7\alpha,17\beta$)-7-ethenyl-17-hydroxyestr-4-en-3-one (34.46 g).

- iii) - A mixture of the product obtained in the previous step (66.24 g), trimethyl orthoformate (80 ml), copper(II) bromide (65.18 g), and methanol (1788 ml) was heated under reflux for 50 min. After cooling, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the residu dissolved in ethyl acetate. The resulting solution was washed 5 with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,17 β)-7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-ol (42.90 g).
- iv) - Following a procedure analogous to that described under v of Example 5, the product obtained in the previous step (41.1 g) was converted to (7 α)-7-ethenyl-3-methoxyestra-10 1,3,5(10)-trien-17-one (38.1 g).
- v) - Following a procedure analogous to that described under i of Example 7, the product obtained in the previous step (36.05 g) was converted to (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (41.37 g).
- vi) - Following a procedure analogous to that described under ii of Example 7, the product 15 obtained in the previous step (20.0 g) was converted to (7 α ,16 α)-16-bromo-7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (28.05 g).
- vii) - Following a procedure analogous to that described under iii of Example 7, the product obtained in the previous step (28.05 g) was converted to (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one cyclic 1,2-ethanediyl acetal (13.93 g).
- viii) - Following a procedure analogous to that described under iv of Example 7, the product 20 obtained in the previous step (31.47 g) was converted to (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one (23.92 g).
- ix) - A solution of the ketone obtained in the previous step (23.92 g) and *p*-toluenesulfonic acid (13.5 g) in toluene (970 ml) was heated under reflux for 15 min. After cooling, the reaction 25 mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into ethyl acetate; the combined organic phases were washed and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10),14-tetraen-17-one (14.9 g) and (7 α ,14 β)-7-ethenyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one (7.32 g).
- x) - Sodium borohydride (8.54 g) was added to a solution of (7 α)-7-ethenyl-3-methoxyestra-1,3,5(10),14-tetraen-17-one (8.72 g) in a mixture of tetrahydrofuran (161 ml), ethanol (161 ml), and water (26.4 ml). The reaction mixture was stirred at room temperature for 50 min. and 30

then poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with water, a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded $(7\alpha,17\beta)$ -7-ethenyl-3-methoxyestra-1,3,5(10),14-tetraen-17-ol (8.45 g).

5

xii) - Following a procedure analogous to that described under i of Example 4, using Pd/C 10 %, the product obtained in the previous step (4.0 g) was converted to $(7\alpha,14\beta,17\beta)$ -7-ethyl-3-methoxyestra-1,3,5(10)-trien-17-ol (3.57 g).

10

xiii) - Following a procedure analogous to that described under v of Example 5, the product obtained in the previous step (3.57 g) was converted to $(7\alpha,14\beta)$ -7-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (2.65 g).

xiv) - Following a procedure analogous to that described under iii of Example 4, the product obtained in the previous step (1.90 g) was converted to $(7\alpha,14\beta)$ -7-ethyl-3-methoxy-17-methyleneestra-1,3,5(10)-triene (2.39 g).

15

xv) - Following a procedure analogous to that described under iv of Example 4, the product obtained in the previous step (2.39 g) was converted to $(7\alpha,14\beta,17\alpha)$ -7-ethyl-3-methoxyestra-1,3,5(10)-triene-17-methanol (2.67 g).

xvi) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (2.67 g) was converted to $(7\alpha,14\beta,17\alpha)$ -7-ethyl-3-methoxyestra-2,5(10)-diene-17-methanol (2.15 g).

20

xvii) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (2.15 g) was converted to $(7\alpha,14\beta,17\alpha)$ -7-ethyl-17-(hydroxymethyl)estr-4-en-3-one (0.60 g), $[\alpha]_D^{20} = +68^\circ$ ($c = 0.50$, dioxane).

25

Example 15

$(7\alpha,14\beta,17\alpha)$ -7-Ethenyl-17-(hydroxymethyl)estr-4-en-3-one.

i) - Following a procedure analogous to that described under xii of Example 6, $(7\alpha,14\beta)$ -7-ethenyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one (Example 14, step ix; 3.18 g) was converted to $(7\alpha,14\beta,17\alpha)$ -7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-ol (2.02 g).

30

ii) - Following a procedure analogous to that described under v of Example 5, the product obtained in the previous step (2.79 g) was converted to $(7\alpha,14\beta)$ -7-ethenyl-3-methoxyestra-1,3,5(10)-trien-17-one (2.44 g).

- iii) - A solution of potassium *tert*-butoxide (7.57 g) in *tert*-butanol (68 ml) was added to a solution of the product obtained in the previous step (2.10 g) in dimethoxyethane (17 ml). A solution of tosylmethyl isocyanide (TosMIC, 2.64 g) in dry dimethoxyethane (34 ml) was added in 1.5 h and the reaction mixture was stirred for 2 h. Then it was poured into a saturated aqueous solution of ammonium chloride. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,17 α)-7-ethenyl-3-methoxyestra-1,3,5(10)-triene-17-carbonitrile (1.91 g).
- iv) - Diisobutylaluminum hydride (20 % solution in toluene, 27.4 ml) was added to a solution of the product obtained in the previous step (1.81 g) in dry toluene (28 ml) while maintaining the temperature below 20 °C. The reaction mixture was stirred for 50 min. and then quenched with aqueous acetic acid (20 %). The resulting mixture was filtered and the filtrate was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7 α ,14 β ,17 α)-7-ethenyl-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde (1.87 g). The product was used in the following step without further purification.
- v) - Following a procedure analogous to that described under ix of Example 6, the product obtained in the previous step (1.87 g) was converted to (7 α ,14 β ,17 α)-7-ethenyl-3-methoxyestra-1,3,5(10)-triene-17-methanol (0.72 g).
- vi) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.72 g) was converted to (7 α ,14 β ,17 α)-7-ethenyl-3-methoxyestra-2,5(10)-diene-17-methanol (0.71 g).
- vii) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.71 g) was converted to (7 α ,14 β ,17 α)-7-ethenyl-17-(hydroxymethyl)estr-4-en-3-one (0.095 g), $[\alpha]_D^{20} = -5.3^\circ$ ($c = 0.75$, dioxane).

*3) 7,20-Substituted compounds***Example 16**

(7 α ,14 β ,17 α ,20S)-20-Hydroxy-7-methyl-19-norpregn-4-en-3-one (a) and (7 α ,14 β ,17 α ,20R)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (b).

- 5 i) - Pyridinium chlorochromate (10.1 g) was added to a solution of (7 α ,14 β ,17 α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (Example 4, step iv; 5.90 g) in dichloromethane (295 ml) containing sodium acetate (8.85 g) and silica (17.7 g). After 3 h stirring at room temperature the reaction mixture was filtered over dicalite and the filtrate was concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,17 α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-carboxaldehyde (4.16 g).
- 10 ii) - Methylmagnesium chloride (3 M solution in tetrahydrofuran, 1.65 ml) was added dropwise to a solution of the aldehyde obtained in the previous step (1.40 g) in dry tetrahydrofuran (42 ml), cooled to 0 °C. After 30 min. stirring, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7 α ,14 β ,17 α ,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.53 g) and (7 α ,14 β ,17 α ,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.40 g).
- 15 iii) - Following a procedure analogous to that described under v of Example 11, (7 α ,14 β ,17 α ,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.53 g) was converted to (7 α ,14 β ,17 α ,20S)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.50 g).
- 20 iiib) - Following a procedure analogous to that described above, (7 α ,14 β ,17 α ,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.40 g) was converted to (7 α ,14 β ,17 α ,20R)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.39 g).
- 25 iva) - Following a procedure analogous to that described under iv of Example 1, (7 α ,14 β ,17 α ,20S)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.50 g) was converted to (7 α ,14 β ,17 α ,20S)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (0.22 g), m.p. 157-160 °C.
- ivb) - Following a procedure analogous to that described under iv of Example 1, (7 α ,14 β ,17 α ,20R)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.39 g) was converted to (7 α ,14 β ,17 α ,20R)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (0.22 g), $[\alpha]_D^{20} = +75^\circ$ ($c = 0.5$, dioxane).

Example 17

[7 α ,14 β ,17 α (S)]-17-(1-Hydroxypropyl)-7-methylestr-4-en-3-one (a) and

[7 α ,14 β ,17 α (R)]-17-(1-hydroxypropyl)-7-methylestr-4-en-3-one (b).

i) - Boron trifluoride diethyl etherate (0.60 ml) was added to a mixture of (7 α ,14 β ,17 α)-17-

5 (hydroxymethyl)-7-methylestr-4-en-3-one (Example 4; 15.5 g), 1,2-ethanedithiol (17 ml), and dry methanol (150 ml). After 2 h stirring at room temperature, a saturated aqueous solution of sodium hydrogencarbonate (50 ml) was added and the methanol was removed under reduced pressure. The product was extracted into ethyl acetate; the combined organic phases were washed with aqueous sodium hydroxide (10 %), water and brine, dried over sodium sulfate and 10 concentrated under reduced pressure. Column chromatography gave (7 α ,14 β ,17 α)-17-(hydroxymethyl)-7-methylestr-4-en-3-one cyclic 1,2-ethanediyil dithioacetal (12.0 g).

ii) - A solution of the product obtained in the previous step (6.0 g) in dry dichloromethane (60 ml), containing dry pyridine (1 ml) was treated with pyridinium dichromate (6.0 g) and the reaction mixture was stirred at room temperature for 1 h. Additional pyridinium dichromate

15 (6.0 g) was added and stirring was continued overnight. Silica (10 g) was added and after 10 min. stirring the mixture was filtered over silica. The residue was washed with ethyl acetate. The filtrate was washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Trituration of the residue and column chromatography of the mother liquor gave (7 α ,14 β ,17 α)-17-formyl-7-methylestr-4-en-3-one cyclic 3-(1,2-ethanediyil dithioacetal) 20 (4.2 g).

iii) - Following a procedure analogous to that described under ii of Example 16, the product obtained in the previous step (1.0 g) was reacted with ethylmagnesium bromide, to give, after chromatography, [7 α ,14 β ,17 α (S)]-17-(1-hydroxypropyl)-7-methylestr-4-en-3-one cyclic 1,2-ethanediyil dithioacetal (0.31 g) and [7 α ,14 β ,17 α (R)]-17-(1-hydroxypropyl)-7-methylestr-4-en-25 3-one cyclic 1,2-ethanediyil dithioacetal (0.075 g).

iva) - A solution of periodic acid (0.028 g) in a mixture of methanol and water (1:1, 2.24 ml) was added to a solution of [7 α ,14 β ,17 α (S)]-17-(1-hydroxypropyl)-7-methylestr-4-en-3-one cyclic 1,2-ethanediyil dithioacetal (0.15 g) in dichloromethane (0.70 ml). After 3 h stirring at room temperature, solid sodium hydrogencarbonate (1 g), solid sodium thiosulfate (1 g), and

30 water (5 ml) were added and the mixture was filtered. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded [7 α ,14 β ,17 α (S)]-17-

(1-hydroxypropyl)-7-methylestr-4-en-3-one (0.069 g), ^1H NMR (CDCl_3) δ 5.80 (m, 1H), 3.47 (m, 1H), 1.25 (s, 3H), 0.95 (t, 3H, J = 7.4 Hz), 0.83 (d, 3H, J = 7.0 Hz).

ivb) - Following a procedure analogous to that described under iva, [$7\alpha,14\beta,17\alpha(\text{R})$]-17-(1-hydroxypropyl)-7-methylestr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (0.075 g) was converted to [$7\alpha,14\beta,17\alpha(\text{R})$]-17-(1-hydroxypropyl)-7-methylestr-4-en-3-one (0.034 g), ^1H NMR (CDCl_3) δ 5.80 (m, 1H), 3.66 (m, 1H), 1.07 (s, 3H), 0.95 (t, 3H, J = 7.4 Hz), 0.85 (d, 3H, J = 7.0 Hz).

Example 18

- 10 In a manner analogous to the procedures described in Example 17, and using ($7\alpha,14\beta,17\alpha$)-17-formyl-7-methylestr-4-en-3-one cyclic 3-(1,2-ethanediyl dithioacetal) (Example 17, step ii) as starting material, the following products were prepared:
- a) - [$7\alpha,14\beta,17\alpha(\text{S})$]-17-(1-Hydroxy-2-propenyl)-7-methylestr-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.86 (m, 1H), 5.81 (m, 1H), 5.19 (dm, 1H, J = 17.1 Hz), 5.07 (dm, 1H, J = 10.3 Hz), 4.02 (m, 1H), 1.26 (s, 3H), 0.83 (d, 3H, J = 7.0 Hz).
- 15 b) - [$7\alpha,14\beta,17\alpha(\text{R})$]-17-(1-Hydroxy-2-propenyl)-7-methylestr-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.92 (m, 1H), 5.80 (m, 1H), 5.22 (dm, 1H, J = 17.2 Hz), 5.11 (d, 1H, J = 10.3 Hz), 4.10 (m, 1H), 1.07 (s, 3H), 0.84 (d, 3H, J = 7.0 Hz).
- c) - [$7\alpha,14\beta,17\alpha(\text{R})$]-17-(1-Hydroxy-2-propynyl)-7-methylestr-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.81 (m, 1H), 4.33 (m, 1H), 2.46 (d, 1H, J = 2.0 Hz), 1.22 (s, 3H), 0.84 (d, 3H, J = 7.1 Hz).
- 20 d) - [$7\alpha,14\beta,17\alpha(\text{S})$]-17-(1-Hydroxy-2-propynyl)-7-methylestr-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.81 (m, 1H), 4.29 (m, 1H), 2.54 (d, 1H, J = 2.0 Hz), 1.24 (s, 3H), 0.84 (d, 3H, J = 7.1 Hz).
- 25 e) - ($7\alpha,14\beta,17\alpha,20\text{S}$)-20-Hydroxy-7-methyl-19,21-dinorchol-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.80 (m, 1H), 3.54 (m, 1H), 1.25 (s, 3H), 0.93 (t, 3H, J = 7.2 Hz), 0.83 (d, 3H, J = 7.0 Hz).
- f) - ($7\alpha,14\beta,17\alpha,20\text{R}$)-20-Hydroxy-7-methyl-19,21-dinorchol-4-en-3-one.
 ^1H NMR (CDCl_3) δ 5.80 (m, 1H), 3.77 (m, 1H), 1.07 (s, 3H), 0.93 (t, 3H, J = 7.1 Hz), 0.84 (d, 3H, J = 7.0 Hz).
- 30 g) - ($7\alpha,14\beta,17\alpha,20\text{S}$)-20-Hydroxy-7-methyl-19,21-dinorchola-4,23-dien-3-one.

¹H NMR (CDCl₃) δ 5.87-5.79 (m, 2H), 5.20-5.14 (m, 2H), 3.56 (m, 1H), 1.25 (s, 3H), 0.83 (d, 3H, J = 7.0 Hz).

h) - (7α,14β,17α,20R)-20-Hydroxy-7-methyl-19,21-dinorchola-4,23-dien-3-one.

¹H NMR (CDCl₃) δ 5.86-5.79 (m, 2H), 5.16-5.11 (m, 2H), 3.80 (m, 1H), 1.07 (s, 3H), 0.84 (d, 3H, J = 7.0 Hz).

5

i) - (7α,14β,17α,20S)-20-Hydroxy-7-methyl-22,24-cyclo-19,21-dinorchol-4-en-3-one.

¹H NMR (CDCl₃) δ 5.80 (m, 1H), 2.81 (td, 1H, J = 8.9 and 3.0 Hz), 1.25 (s, 3H), 0.89 (m, 1H), 0.83 (d, 3H, J = 7.0 Hz), 0.57 (m, 1H), 0.44 (m, 1H), 0.32 (m, 1H), 0.22 (m, 1H).

10 j) - (7α,14β,17α,20R)-20-Hydroxy-7-methyl-22,24-cyclo-19,21-dinorchol-4-en-3-one.

¹H NMR (CDCl₃) δ 5.80 (m, 1H), 2.91 (dd, 1H, J = 8.9 and 4.0 Hz), 1.08 (s, 3H), 1.00 (m, 1H), 0.85 (d, 3H, J = 7.0 Hz), 0.55 (m, 2H), 0.33 (m, 1H), 0.25 (m, 1H).

k) - (7α,14β,17α,20R)-21,21,21-Trifluoro-20-hydroxy-7-methyl-19-norpregn-4-en-3-one.

¹H NMR (CDCl₃) δ 5.81 (m, 1H), 3.89 (m, 1H), 1.28 (s, 3H), 0.84 (d, 3H, J = 7.0 Hz).

15 l) - (7α,14β,17α,20S)-21,21,21-Trifluoro-20-hydroxy-7-methyl-19-norpregn-4-en-3-one.

¹H NMR (CDCl₃) δ 5.81 (m, 1H), 4.08 (m, 1H), 1.07 (s, 3H), 0.85 (d, 3H, J = 7.0 Hz).

Example 19

(7α,14β,17α)-20-Hydroxy-7,20-dimethyl-19-norpregn-4-en-3-one.

20 i) - Following a procedure analogous to that described under ii of Example 4, a mixture (1:1) of (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol and (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (Example 16, step ii; 1.04 g) was converted to (7α,14β,17α)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-one (0.85 g).

25 ii) - Following a procedure analogous to that described under ii of Example 16, the ketone obtained in the previous step (0.85 g) was converted to (7α,14β,17α)-3-methoxy-7,20-dimethyl-19-norpregna-1,3,5(10)-trien-20-ol (0.90 g).

iii) - Following a procedure analogous to that described under v of Example 4, the product obtained in the previous step (0.90 g) was converted to (7α,14β,17α)-3-methoxy-7,20-dimethyl-19-norpregna-2,5(10)-dien-20-ol (0.90 g).

30

iv) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.90 g) was converted to (7 α ,14 β ,17 α)-20-hydroxy-7,20-dimethyl-19-norpregn-4-en-3-one (0.45 g). M.p. 179-181 °C.

5 Example 20

In a manner analogous to the procedures described under ii of Example 16, v of Example 4, and iv of Example 1, respectively, and using (7 α ,14 β ,15 β ,16 β ,17 α)-3-methoxy-7-methyl-15,16-methyleneestra-1,3,5(10)-triene-17-carboxaldehyde (Example 10, step iii) as starting material, the following products were prepared:

- 10 a) - (7 α ,14 β ,15 β ,16 β ,17 α ,20S)-20-Hydroxy-7-methyl-15,16-methylene-19-norpregn-4-en-3-one. M.p. 160-165 °C.
 b) - (7 α ,14 β ,15 β ,16 β ,17 α ,20R)-20-Hydroxy-7-methyl-15,16-methylene-19-norpregn-4-en-3-one. $[\alpha]_D^{20} = +61.2^\circ$ (c = 0.515, dioxane).

15 Example 21

(7 α ,14 β ,15 β ,16 β ,17 α)-20-Hydroxy-7,20-dimethyl-15,16-methylene-19-norpregn-4-en-3-one.

The title compound was prepared from (7 α ,14 β ,15 β ,16 β ,17 α)-3-methoxy-7-methyl-15,16-methyleneestra-1,3,5(10)-triene-17-carboxaldehyde (Example 10, step iii) in a manner analogous to the procedures described under ii of Example 16, v of Example 5, ii of Example 16, viii of Example 5, and iv of Example 1, respectively. M.p. 158.5-161.8 °C.

4) 10-Substituted compounds

Example 22

(14 β ,17 α)-17-[(Acetoxy)methyl]androst-4-en-3-one (a) and (14 β ,17 α)-17-

25 (Hydroxymethyl)androst-4-en-3-one (b).

- i) - A solution of (3 β)-3-(acetoxy)androsta-5,14-dien-17-one [Andre, A.F.St. *et al*, J. Am. Chem. Soc. 74, 5506 (1952); 42.9 g] in dry ethanol (429 ml) was cooled to -10 °C. Sodium borohydride (1.51 g) in dry ethanol (33.5 ml) was added and the mixture was stirred at -10 °C for 7.5 h. Excess sodium borohydride was destroyed by careful addition of an aqueous solution of acetic acid (50 %). The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated. Column chromatography provided (3 β ,17 β)-androsta-5,14-diene-3,17-diol 3-acetate (19.5 g).

ii) - A solution of the product obtained in the previous step (20.0 g) in dry ethanol (500 ml), containing palladium on activated carbon (10 %; 8.0 g), was stirred under hydrogen (3 bar) at room temperature for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, to give ($3\beta,14\beta,17\beta$)-androst-5-ene-3,17-diol 3-acetate (20.2 g). The
5 product was used in the following step without further purification.

iii) - Following a procedure analogous to that described under v of Example 5, the product obtained in the previous step (1.50 g) was converted to ($3\beta,14\beta$)-3-(acetoxy)androst-5-en-17-one (1.08 g).

iv) - A solution of the ketone obtained in the previous step (1.08 g) in tetrahydrofuran (11.6 ml)

10 and methanol (10.4 ml) was treated with a solution of potassium hydroxide (0.589 g) in water (3.51 ml). The reaction mixture was stirred overnight and then poured into brine. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give ($3\beta,14\beta$)-3-hydroxyandrost-5-en-17-one (1.06 g). The product was used in the next step without further
15 purification.

v) - Following a procedure analogous to that described under iii of Example 5, the alcohol obtained in the previous step (1.06 g) was converted to ($3\beta,14\beta$)-3-[($(1,1$ -dimethylethyl)dimethylsilyl]oxy]androst-5-en-17-one (1.70 g).

vi) - Following a procedure analogous to the procedure described under iii of Example 4, the ketone obtained in the previous step (1.70 g) was converted to ($3\beta,14\beta$)-3-[($(1,1$ -dimethylethyl)dimethylsilyl]oxy]-17-methyleneandrost-5-ene (1.41 g).

vii) - Following a procedure analogous to the procedure described under iv of Example 4, the product obtained in the previous step (1.41 g) was converted to ($3\beta,14\beta,17\alpha$)-3-[($(1,1$ -dimethylethyl)dimethylsilyl]oxy]androst-5-ene-17-methanol (2.28 g).

25 viii) - A solution of the alcohol obtained in the previous step (2.28 g) in dry pyridine (3.38 ml) was treated with acetic anhydride (1.74 ml) and the mixture was stirred at room temperature for 1 h. Water was added and stirring was continued for another 1 h. The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under
30 reduced pressure, to give ($3\beta,14\beta,17\alpha$)-3-[($(1,1$ -dimethylethyl)dimethylsilyl]oxy]-17-[(acetoxy)methyl]androst-5-ene (1.43 g). The product was used in the next step without further purification.

- ix) - Following a procedure analogous to the procedure described under iv of Example 1, the product obtained in the previous step (1.43 g) was converted to (3 β ,14 β ,17 α)-17-[(acetoxy)methyl]androst-5-en-3-ol (0.78 g).
- 5 x) - A mixture of the product obtained in the previous step (0.774 g) and aluminium isopropoxide (0.64 g) in dry toluene (9.2 ml) and 2-butanone (5.6 ml) was heated under reflux for 1 h. After cooling, a solution of potassium sodium tartrate tetrahydrate (4.4 g) in water (6 ml) was added and the mixture was stirred at room temperature for 30 min. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography 10 afforded (14 β ,17 α)-17-[(acetoxy)methyl]androst-4-en-3-one (0.44 g), m.p. 141-142 °C.
- xi) - Following a procedure analogous to that described under iv, (14 β ,17 α)-17-[(acetoxy)methyl]androst-4-en-3-one (0.32 g) was converted to (14 β ,17 α)-17-(hydroxymethyl)androst-4-en-3-one (0.10 g), m.p. 125.1-127.6 °C.

15 5) 15-Substituted compounds

Example 23

(14 β ,15 β ,17 α)-17-(Hydroxymethyl)-15-methylestr-4-en-3-one.

Following procedures analogous to those described under v-ix of Example 7, (14 β ,15 β ,17 α)-17-(hydroxymethyl)-15-methylestr-4-en-3-one was prepared from (14 β)-3-methoxyestra-20,1,3,5(10),15-tetraen-17-one [Johnson, J. et al, J. Amer. Chem. Soc. 79, 2005 (1957)]. $[\alpha]_D^{20} = +3.9^\circ$ ($c = 1.20$, dioxane).

6) 20-Substituted compounds

Example 24

25 (14 β ,17 α ,20S)-20-Hydroxy-19-norpregn-4-en-3-one (a) and (14 β ,17 α ,20R)-20-hydroxy-19-norpregn-4-en-3-one (b).

i) - A solution of sulfur trioxide pyridine complex (50.0 g) in dimethyl sulfoxide (250 ml) was added in 15 min. to a solution of (14 β ,17 α)-3-methoxyestra-1,3,5(10)-triene-17-methanol (Example 1, step ii; 23.6 g) in a mixture of dimethyl sulfoxide (425 ml) and triethylamine (70 ml). After 20 min. stirring, 2-propanol (88 ml) was added and stirring was continued for 15 min. The reaction mixture was poured into water (1300 ml) and the product was extracted into dichloromethane. The combined organic phases were washed with water and brine, dried over

magnesium sulfate and concentrated under reduced pressure. Trituration (water/ethanol, first 3:2, then 1:1) afforded ($14\beta,17\alpha$)-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde (18.8 g).

ii) - Following a procedure analogous to that described under ii of Example 16, the product obtained in the previous step (3.5 g) was converted to ($14\beta,17\alpha,20S$)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.78 g) and ($14\beta,17\alpha,20R$)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.16 g).

iii) - Following a procedure analogous to that described under iii of Example 1, ($14\beta,17\alpha,20S$)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.5 g) was converted to ($14\beta,17\alpha,20S$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.59 g).

ivb) - Following a procedure analogous to that described above, ($14\beta,17\alpha,20R$)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.0 g) was converted to ($14\beta,17\alpha,20R$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.13 g).

iva) - Following a procedure analogous to that described under iv of Example 1, ($14\beta,17\alpha,20S$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.42 g) was converted to ($14\beta,17\alpha,20S$)-20-hydroxy-19-norpregn-4-en-3-one (0.84 g), m.p. 152-153 °C.

ivb) - Following a procedure analogous to that described above, ($14\beta,17\alpha,20R$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.13 g) was converted to ($14\beta,17\alpha,20R$)-20-hydroxy-19-norpregn-4-en-3-one (0.72 g), m.p. 108-109.5 °C.

20 Example 25

In a manner analogous to the procedures described in Example 24, and using ($14\beta,17\alpha$)-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde (Example 24, step i) as starting material, the following products were prepared:

a) - [$14\beta,17\alpha(S)$]-17-(1-Hydroxypropyl)estr-4-en-3-one.

25 M.p. 122-123 °C.

b) - [$14\beta,17\alpha(R)$]-17-(1-Hydroxypropyl)estr-4-en-3-one.

M.p. 120-121 °C.

c) - ($14\beta,17\alpha,20S$)-20-Hydroxy-19,21-dinorchol-4-en-3-one.

M.p. 102-102.5 °C.

30 d) - ($14\beta,17\alpha,20R$)-20-Hydroxy-19,21-dinorchol-4-en-3-one.

¹H NMR δ 5.81 (m, 1H), 3.76 (m, 1H), 1.08 (s, 3H), 0.92 (t, 3H, J = 7.0 Hz).

Example 26

In a manner analogous to the procedures described in Example 17, and using ($14\beta,17\alpha$)-17-(hydroxymethyl)estr-4-en-3-one (Example 1) as starting material, the following products were

5 prepared:

a) - $[14\beta,17\alpha(R)]$ -17-(1-Hydroxy-2-propynyl)estr-4-en-3-one.

^1H NMR (CDCl₃) δ 5.82 (m, 1H), 4.34 (m, 1H), 2.46 (d, 1H, J = 2.0 Hz), 1.21 (s, 3H).

b) - $[14\beta,17\alpha(S)]$ -17-(1-Hydroxy-2-propynyl)estr-4-en-3-one.

^1H NMR (CDCl₃) δ 5.82 (m, 1H), 4.29 (m, 1H), 2.54 (d, 1H, J = 2.4 Hz), 1.24 (s, 3H).

10 c) - ($14\beta,17\alpha,20R$)-21,21,21-Trifluoro-20-hydroxy-19-norpregn-4-en-3-one.

^1H NMR (CDCl₃) δ 5.83 (m, 1H), 3.91 (m, 1H), 1.27 (s, 3H).

d) - ($14\beta,17\alpha,20S$)-21,21,21-Trifluoro-20-hydroxy-19-norpregn-4-en-3-one.

^1H NMR (CDCl₃) δ 5.83 (m, 1H), 4.09 (m, 1H), 1.07 (s, 3H).

e) - $[14\beta,17\alpha(R)]$ -17-[(Hydroxy)(phenyl)methyl]estr-4-en-3-one.

^1H NMR (CDCl₃) δ 7.34 (m, 4H), 7.29 (m, 1H), 5.81 (m, 1H), 4.65 (dd, 1H, J = 6.7 and 3.1 Hz), 0.61 (s, 3H).

f) - $[14\beta,17\alpha(S)]$ -17-[(Hydroxy)(phenyl)methyl]estr-4-en-3-one.

^1H NMR (CDCl₃) δ 7.33 (m, 4H), 7.27 (m, 1H), 5.82 (m, 1H), 4.55 (dd, 1H, J = 10.2 and 3.5 Hz), 1.36 (s, 3H).

20

Example 27

($14\beta,17\alpha,20S$)-20-Hydroxy-19-norpregna-4,9-dien-3-one (a) and ($14\beta,17\alpha,20R$)-20-hydroxy-19-norpregna-4,9-dien-3-one (b).

i) - Following a procedure analogous to that described for Example 2, a mixture of ($14\beta,17\alpha$

25 , $20S$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol and ($14\beta,17\alpha,20R$)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (Example 24, step **iiia** and **iiib**, respectively; ratio 1:1; 7.87 g) was converted to a mixture of ($14\beta,17\alpha,20S$)-20-hydroxy-19-norpregn-5(10)-en-3-one and ($14\beta,17\alpha,20R$)-20-hydroxy-19-norpregn-5(10)-en-3-one (7.5 g; ratio 1:1).

ii) - Following a procedure analogous to that described in Example 3, the mixture obtained in

30 the previous step (7.5 g) was converted to ($14\beta,17\alpha,20S$)-20-hydroxy-19-norpregna-4,9-dien-3-one (2.4 g), m.p. 147-148 °C, and ($14\beta,17\alpha,20R$)-20-hydroxy-19-norpregna-4,9-dien-3-one (1.95 g), m.p. 118-119 °C.

7) 11,20-Substituted compounds

Example 28

(11 β ,14 β ,17 α ,20S)-11-Ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (a) and (11 β ,14 β ,17 α ,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (b).

5 i) - A solution of (11 β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one [Pomper, M.G. *et al*, J. Med. Chem. 33, 3143 (1990); 15 g] in a mixture of tetrahydrofuran (50 ml), ethylene glycol (30 ml), and triethyl orthoformate (30 ml) was treated with *p*-toluenesulfonic acid (0.25 g) and the reaction mixture was stirred at room temperature overnight. Sodium hydrogencarbonate (1 g) was added and after 10 min. stirring the mixture was concentrated under reduced pressure. Then it was poured into an aqueous solution of sodium hydrogencarbonate (5 %, 200 ml) and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (11 β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (16.2 g).

10 ii) - Following a procedure analogous to that described under ii of Example 7, the product obtained in the previous step (16.0 g) was converted to (11 β ,16 α)-16-bromo-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (18.5 g).

15 iii) - Following a procedure analogous to that described under iii of Example 7, the bromide obtained in the previous step (18.0 g) was converted to (11 β)-11-ethyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one cyclic 1,2-ethanediyl acetal (13.0 g).

20 iv) - Following a procedure analogous to that described under iv of Example 7, the product obtained in the previous step (13.0 g) was converted to (11 β)-11-ethyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one (7.6 g).

25 v) - A solution of the ketone obtained in the previous step (8.5 g) and *p*-toluenesulfonic acid (0.20 g) in isopropenyl acetate (75 ml) was heated under reflux for 30 min. The reaction medium was partially (25 ml) distilled off and replaced by fresh isopropenyl acetate (25 ml). Heating was continued for another 30 min., an aqueous solution of sodium hydrogencarbonate (10 %) was added, and the mixture was concentrated. The product was extracted into diethyl ether; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was taken up in a mixture of tetrahydrofuran (75 ml), ethanol (75 ml) and water (10 ml). Sodium borohydride (2 g) was added and the

mixture was stirred at room temperature for 1 h. Excess sodium borohydride was destroyed by careful addition of acetone (25 ml). The mixture was concentrated, water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. Column chromatography provided (11 β ,17 β)-11-ethyl-3-methoxyestra-1,3,5(10),14-tetraen-17-ol (8.0 g).

5 vi) - A mixture of the product obtained in the previous step (6.2 g) and palladium on activated carbon (5 %; 1.0 g) in ethanol (100 ml) was stirred under hydrogen (1 bar) at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, to give (11 β ,14 β ,17 β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-ol (6.0 g). The 10 product was used in the following step without further purification.

vii) - Following a procedure analogous to that described under i of Example 16, the product obtained in the previous step (6.0 g) was converted to (11 β ,14 β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (4.7 g)..

15 viii) - Following a procedure analogous to that described under iii of Example 4, the product obtained in the previous step (1.0 g) was converted to (11 β ,14 β)-11-ethyl-3-methoxy-17-methyleneestra-1,3,5(10)-triene (1.0 g).

ix) - Following a procedure analogous to that described under iv of Example 4, the product obtained in the previous step (4.0 g) was converted to (11 β ,14 β ,17 α)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-methanol (3.5 g).

20 x) - Following a procedure analogous to that described under iii of Example 1, the product obtained in the previous step (3.2 g) was converted to (11 β ,14 β ,17 α)-11-ethyl-3-methoxyestra-2,5(10)-diene-17-methanol (3.3 g).

xi) - A solution of (11 β ,14 β ,17 α)-11-ethyl-3-methoxyestra-2,5(10)-diene-17-methanol (3.3 g) in tetrahydrofuran (30 ml) was treated with hydrochloric acid (2 M, 10 ml). The reaction 25 mixture was stirred at room temperature for 30 min. and then neutralized with a saturated aqueous solution of sodium hydrogencarbonate. Water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give (11 β ,14 β ,17 α)-11-ethyl-17-(hydroxymethyl)estr-5(10)-en-3-one (3.3 g). The product was used in the following step 30 without further purification.

xii) - A solution of the ketone obtained in the previous step (3.3 g) and *p*-toluenesulfonic acid (0.1 g) in methanol (30 ml) and trimethyl orthoformate (6 ml) was stirred at room temperature

for 15 min. Solid sodium hydrogencarbonate (1 g) was added and stirring was continued for another 15 min. The reaction mixture was partially concentrated, an aqueous solution of sodium hydrogencarbonate (5 %) was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography provided (11 β ,14 β ,17 α)-11-ethyl-3,3-dimethoxyestr-5(10)-ene-17-methanol (3.0 g).

xiii) - A solution of oxalyl chloride (1 ml) in dichloromethane (60 ml) was cooled to -60 °C. Dimethyl sulfoxide (1.64 ml) was added and the mixture was stirred for 5 min. A solution of the compound obtained in the previous step (2.6 g) in dichloromethane (5 ml) was added and stirring was continued for 20 min. Triethylamine (5 ml) was added and the temperature was allowed to rise to 0 °C in 20 min. Water (50 ml) was added and the product was extracted into diethyl ether. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (11 β ,14 β ,17 α)-11-ethyl-3,3-dimethoxyestr-5(10)-ene-17-carboxaldehyde (2.4 g).

xiv) - Following a procedure analogous to that described under ii of Example 16, the product obtained in the previous step (2.4 g) was converted to (11 β ,14 β ,17 α ,20S)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (1.25 g) and (11 β ,14 β ,17 α ,20R)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (0.90 g).

xva) - A solution of (11 β ,14 β ,17 α ,20S)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (1.25 g) in tetrahydrofuran (12 ml) was treated with hydrochloric acid (0.6 M, 2 ml). The reaction mixture was stirred at room temperature for 30 min. and then neutralized with a saturated aqueous solution of sodium hydrogencarbonate. Water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Crystallization gave (11 β ,14 β ,17 α ,20S)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (0.85 g), m.p. 177-178 °C.

xvb) - Following a procedure analogous to that described under xva, (11 β ,14 β ,17 α ,20R)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (0.90 g) was converted to (11 β ,14 β ,17 α ,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (0.68 g), 1 H NMR δ 3.89 (m, 1H), 2.77 (m, 2H), 1.26 (d, 3H, J = 6.2 Hz), 1.18 (s, 3H), 0.89 (t, 3H, J = 6.8 Hz).

Example 29

In a manner analogous to the procedure described under iv of Example 1, the following products were prepared:

- a) - (11 β ,14 β ,17 α ,20S)-11-Ethyl-20-hydroxy-19-norpregn-4-en-3-one from
5 (11 β ,14 β ,17 α ,20S)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (Example 28a).
[α]_D²⁰ = +82.4 ° (c = 0.71, dioxane).
- b) - (11 β ,14 β ,17 α ,20R)-11-Ethyl-20-hydroxy-19-norpregn-4-en-3-one from
(11 β ,14 β ,17 α ,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (Example 28b).
M.p. 185-186 °C.

10

Example 30

(11 β ,14 β ,17 α ,20S)-11-Ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one.

i) - Following a procedure analogous to that described under i of Example 28, (14 β ,17 α ,20S)-20-hydroxy-19-norpregna-4,9-dien-3-one (Example 27a; 2.5 g) was converted to (14 β ,17 α ,20S)-20-hydroxy-19-norpregna-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (1.5 g).

ii) - A solution of the product obtained in the previous step (1.5 g) in dry dichloromethane (15 ml), containing sodium hydrogencarbonate (3 g), was cooled to -15 °C. m-Chloroperbenzoic acid (60 %, 1.42 g) in dry dichloromethane (12.5 ml) was added in 10 min. and the reaction mixture was stirred at -10 °C for 1.25 h. Then it was poured into a mixture of a saturated aqueous solution of sodium hydrogencarbonate (53 ml) and an aqueous solution of sodium hydrogensulfite (5 %, 12.5 ml) and the product was extracted into dichloromethane. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate, water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give (5 α ,10 α ,14 β ,17 α ,20S)-5,10-epoxy-20-hydroxy-19-norpregn-9(11)-en-3-one cyclic 1,2-ethanediyl acetal (1.6 g).

iii) - A solution of the epoxide obtained in the previous step (1.6 g) in dry tetrahydrofuran (15 ml), containing copper(I) chloride (0.20 g), was cooled to 0 °C and treated with a solution of vinylmagnesium bromide in tetrahydrofuran (15 %, 12.7 ml). After 1 h stirring at 0 °C the reaction mixture was poured into an aqueous solution of ammonium chloride (10 %). The product was extracted into dichloromethane; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column

chromatography afforded ($5\alpha,11\beta,14\beta,17\alpha,20S$)-11-ethenyl-5,20-dihydroxy-19-norpregn-9-en-3-one cyclic 1,2-ethanediyl acetal (0.65 g).

iv) - Following a procedure analogous to that described under iv of Example 1, the product obtained in the previous step (0.60 g) was converted to (11 β ,14 β ,17 α ,20S)-11-ethenyl-20-

5 hydroxy-19-norpregna-4,9-dien-3-one (0.28 g), m.p. 144.5-146.1 °C.

Example 31

(11 β ,14 β ,17 α ,20R)-11-Ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one.

10 In a manner analogous to the procedures described in Example 30, ($14\beta,17\alpha,20R$)-20-hydroxy-19-norpregna-4,9-dien-3-one (Example 27b) was converted to (11 β ,14 β ,17 α ,20R)-11-ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one. M.p. 96.3-97.2 °C.

8) 18,20-Substituted compounds

Example 32

Following procedures analogous to those described in Example 4 and 16, respectively, and using (17β)-13-ethyl-3-methoxygon-1,3,5(10),14-tetraen-17-ol [US 3577410 (1968)] as starting material, the following products were prepared:

a) - (14 β ,17 α ,20S)-13-Ethyl-20-hydroxy-18,19-dinorpregn-4-en-3-one.

20 $[\alpha]_D^{20} = +78.3^\circ$ (c = 0.36, dioxane).

b) - (14 β ,17 α ,20R)-13-Ethyl-20-hydroxy-18,19-dinorpregn-4-en-3-one.

M.p. 110.5-111.5 °C.

c) - [14 β ,17 α (S)]-13-Ethyl-17-(1-hydroxypropyl)gon-4-en-3-one.

$[\alpha]_D^{20} = +64.1^\circ$ (c = 0.34, dioxane).

25 d) - [14 β ,17 α (R)]-13-Ethyl-17-(1-hydroxypropyl)gon-4-en-3-one.

M.p. 89.5-90.5 °C.

e) - [14 β ,17 α (S)]-13-Ethyl-17-(1-hydroxy-2-propenyl)gon-4-en-3-one.

1H NMR δ 5.96-5.76 (m, 2H), 5.25-5.01 (m, 2H), 4.02 (m, 1H), 0.89 (t, 3H, J = 8.0 Hz).

f) - [14 β ,17 α (R)]-13-Ethyl-17-(1-hydroxy-2-propenyl)gon-4-en-3-one.

30 M.p. 128.5-129.5 °C.

9) *Miscellaneous***Example 33**

Following a procedure analogous to that described under viii of Example 22, using ($7\alpha,14\beta,17\alpha$)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (Example 4) as starting material, the following products were prepared:

- a) - ($7\alpha,14\beta,17\alpha$)-17-[(Acetoxy)methyl]-7-methylestr-4-en-3-one.
M.p. 65-68 °C.
- b) - ($7\alpha,14\beta,17\alpha$)-17-[[(2,2-Dimethyl-1-oxopropyl)oxy]methyl]-7-methylestr-4-en-3-one.
 ^1H NMR δ 5.81 (m, 1H), 4.12 (m, 1H), 3.95 (m, 1H), 1.20 (s, 9H), 1.12 (s, 3H), 0.84 (d, 3H, J = 7.4 Hz).
- c) - ($7\alpha,14\beta,17\alpha$)-7-Methyl-17-[[(1-oxoundecyl)oxy]methyl]estr-4-en-3-one.
M.p. 45.5-48.5 °C.
- d) - ($7\alpha,14\beta,17\alpha$)-17-[[[(trans-4-Butylcyclohexyl)carbonyl]oxy]methyl]-7-methylestr-4-en-3-one.
 $[\alpha]_D^{20} = +63.1^\circ$ (c = 0.635, dioxane).
- e) - ($7\alpha,14\beta,17\alpha$)-7-Methyl-17-[[(phenylcarbonyl)oxy]methyl]estr-4-en-3-one.
 ^1H NMR δ 8.03 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 5.81 (m, 1H), 4.40 (m, 1H), 4.22 (m, 1H), 1.18 (s, 3H), 0.85 (d, 3H, J = 7.1 Hz).

Example 34($3\beta,7\alpha,14\beta,17\alpha$)-17-(Hydroxymethyl)-7-methylestr-4-en-3-ol.

Following a procedure analogous to that described under ix of Example 6, the title compound was prepared from ($7\alpha,14\beta,17\alpha$)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (Example 4). $[\alpha]_D^{20} = +28.2^\circ$ (c = 0.49, dioxane).

25

Example 35($3\alpha,7\alpha,14\beta,17\alpha$)-17-(Hydroxymethyl)-7-methylestr-5(10)-en-3-ol.

The title compound (2.27 g) was isolated as side product after Birch reduction and hydrolysis of ($7\alpha,14\beta,17\alpha$)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (Example 4, step iv; 30 22.0 g). M.p. 64-70 °C.

Example 36

(*3E,7 α ,14 β ,17 α*)-3-(Hydroxyimino)-7-methylestr-4-ene-17-methanol (a) and (*3Z,7 α ,14 β ,17 α*)-3-(hydroxyimino)-7-methylestr-4-ene-17-methanol (b).

To a solution of (*7 α ,14 β ,17 α*)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (Example 4; 1.0 g) in pyridine (6 ml) was added hydroxylamine hydrochloride (2.65 g). The reaction mixture was stirred at 80 °C for 1.5 h. After cooling, the mixture was poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (*3E,7 α ,14 β ,17 α*)-3-(hydroxyimino)-7-methylestr-4-ene-17-methanol (0.54 g), $[\alpha]_D^{20} = +95.5^\circ$ (c = 1.41, dioxane), and (*3Z,7 α ,14 β ,17 α*)-3-(hydroxyimino)-7-methylestr-4-ene-17-methanol (0.28 g), $[\alpha]_D^{20} = +87.4^\circ$ (c = 1.0, dioxane).

Example 37

(*7 α ,14 β ,17 α*)-7-Methylestr-4-ene-17-methanol.

(*7 α ,14 β ,17 α*)-17-(Hydroxymethyl)-7-methylestr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (Example 17, step i; 1.11 g) in dry tetrahydrofuran (4 ml) was added to a solution of sodium (0.61 g) in liquid ammonia (70 ml), cooled to -40 °C. After 1 h stirring, dry ethanol was added and the ammonia was allowed to evaporate. Water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with aqueous sodium hydroxide (1 M), water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded (*7 α ,14 β ,17 α*)-7-methylestr-4-ene-17-methanol (0.34 g), $[\alpha]_D^{20} = +56.9^\circ$ (c = 0.93, dioxane).

Results

A plurality of compounds according to the invention were tested for androgenic activity (the procedures for which have been described above) and rated in the Table below according to the following scheme:

- 5 + androgenic activity found;
- ++ high androgenic activity;
- +++ excellent androgenic activity;
- nd no data available

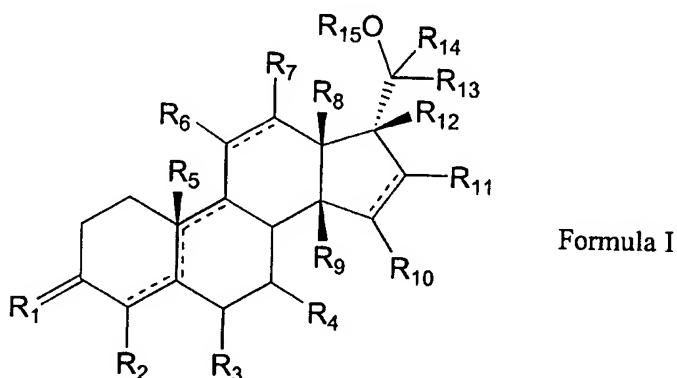
Parent compound of the compounds of the invention is ($14\beta,17\alpha$)-17-(hydroxymethyl)estr-4-en-3-one (Example 1). Compounds in the Table are derivatives of the latter; they all have a carbonyl group at C-3 and a Δ^4 double bond unless otherwise stated.

Table. Androgenic activities of compounds of the invention.

	Example	Rating	Example	Rating
5	<i>Unsubstituted</i>		<i>20-Substituted</i>	
1		+++	24a 20S-Me	++
2	$\Delta^{5(10)}$	++	24b 20R-Me	+
3	$\Delta^{4,9}$	+	25a 20S-Et	++
			25b 20R-Et	+
10	<i>7-Substituted</i>		25c 20S-Pr	+
4	7 α -Me	+++	25d 20R-Pr	nd
5	7 α -Me, $\Delta^{4,15}$	+++	26a 20R-ethynyl	nd
6	7 α -Me, 14 β -Me	++	26b 20S-ethynyl	nd
7	7 α -Me, 15 β -Me	+	26c 20R-CF ₃	nd
15	8 7 α -Me, 16 α -Me	+	26d 20S-CF ₃	nd
9	7 α -Me, 16 β -Me	++	26e 20R-Ph	nd
10	7 α -Me, 15 β , 16 β -CH ₂	++	26f 20S-Ph	nd
11	7 α -Me, 17 β -Me	+	27a $\Delta^{4,9}$, 20S-Me	++
12	7 α -Me, 17 β -F	+++	27b $\Delta^{4,9}$, 20R-Me	+
20	13 7 α -Me, 17 β -OH	+		
14	7 α -Et	+	<i>11,20-Substituted</i>	
15	7 α -Vinyl	++	28a $\Delta^{3(10)}, 11\beta$ -Et, 20S-Me	+
			28b $\Delta^{3(10)}, 11\beta$ -Et, 20R-Me	nd
	<i>7,20-Substituted</i>		29a 11 β -Et, 20S-Me	+
25	16a 7 α -Me, 20S-Me	++	29b 11 β -Et, 20R-Me	+
16b	7 α -Me, 20R-Me	+	30 $\Delta^{4,9}, 11\beta$ -vinyl, 20S-Me	+
17a	7 α -Me, 20S-Et	nd	31 $\Delta^{4,9}, 11\beta$ -vinyl, 20R-Me	+
17b	7 α -Me, 20R-Et	+		
30	18a 7 α -Me, 20S-vinyl	+	<i>18,20-Substituted</i>	
18b	7 α -Me, 20R-vinyl	+	32a 18-Me, 20S-Me	+
18c	7 α -Me, 20R-ethynyl	+	32b 18-Me, 20R-Me	+
18d	7 α -Me, 20S-ethynyl	+	32c 18-Me, 20S-Et	nd
18e	7 α -Me, 20S-Pr	nd	32d 18-Me, 20R-Et	nd
18f	7 α -Me, 20R-Pr	nd	32e 18-Me, 20S-vinyl	nd
35	18g 7 α -Me, 20S-allyl	+	32f 18-Me, 20R-vinyl	nd
18h	7 α -Me, 20R-allyl	+		
18i	7 α -Me, 20S-cyclopropyl	nd	<i>Miscellaneous</i>	
18j	7 α -Me, 20R-cyclopropyl	nd	33a 7 α -Me, acetate	+
18k	7 α -Me, 20R-CF ₃	nd	33b 7 α -Me, diMepropionate	nd
40	18l 7 α -Me, 20S-CF ₃	nd	33c 7 α -Me, undecanoate	+
19	7 α -Me, 20,20-diMe	+	33d 7 α -Me, buciclate	+
20a	7 α -Me, 15 β , 16 β -CH ₂ , 20S-Me	++	33e 7 α -Me, benzoate	nd
20b	7 α -Me, 15 β , 16 β -CH ₂ , 20R-Me	+	34 7 α -Me, 3 β -OH	++
21	7 α -Me, 15 β , 16 β -CH ₂ , 20,20-diMe	+	35 $\Delta^{3(10)}, 7\alpha$ -Me, 3 α -OH	nd
45			36a 7 α -Me, 3E-(NOH)	+
	<i>10-Substituted and 15-Substituted</i>		36a 7 α -Me, 3Z-(NOH)	+
22a	10-Me, acetate	+	37 7 α -Me, 3,3-diH	+
22b	10-Me	+		
23	15 β -Me	+		
50				

Claims:

1. A steroid compound, or a pharmaceutically acceptable salt or ester thereof, characterised by having a hydroxymethyl moiety at carbon atom no. 17 and a $14\beta,17\alpha$ -configuration for use as a medicine, with the proviso that carbon atom number 11 of the steroid skeleton does not carry, as a substituent, a homocyclic or heterocyclic aryl group.
2. A steroid compound satisfying the structural formula:



10

wherein

R₁ is O, (H,H), (H,OR), NOR, with R being hydrogen, (C₁₋₆) alkyl, (C₁₋₆) acyl;

R₂ is hydrogen, (C₁₋₆) alkyl, or halogen;

R₃ is hydrogen, (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl;

15 R₄ is hydrogen, halogen, or cyano; or R₄ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₅ is hydrogen, or (C₁₋₆) alkyl;

R₆ is hydrogen, (C₁₋₆) alkoxy, or halogen; or R₆ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl, a (C₁₋₆) alkylidene group, or a (C₂₋₆) alkenylidene group, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

20 R₇ is hydrogen, or (C₁₋₆) alkyl;

R₈ is (C₁₋₆) alkyl;

R₉ is hydrogen, halogen or cyano; or R₉ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R_{10} is hydrogen, (C_{1-6}) alkoxy, halogen, or cyano; or R_{10} is (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, oxo, halogen, or cyano; or R_{10} together with R_{11} and the carbon atoms at which they are placed form a cyclopropane ring;

5 R_{11} is hydrogen, (C_{1-6}) alkoxy, halogen, or cyano; or R_{11} is (C_{1-6}) alkyl, (C_{2-6}) alkenyl or (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, oxo, halogen, or cyano; or R_{11} together with R_{10} and the carbon atoms at which they are placed form a cyclopropane ring;

10 R_{12} is hydrogen, hydroxy, halogen, or cyano; or R_{12} is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, oxo, halogen, or cyano;

15 R_{13} and R_{14} are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, (C_{1-4}) alkoxy, (C_{1-4}) alkyl or halogen; or R_{13} and R_{14} are independently (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{3-6}) cycloalkyl, (C_{5-6}) cycloalkenyl or (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, phenyl, oxo, halogen, or cyano; or R_{13} and R_{14} together with the carbon atom at which they are placed form a (C_{3-6}) cycloalkane ring or a (C_{5-6}) cycloalkene ring;

R_{15} is hydrogen, SO_3H , (C_{1-6}) alkyl, (C_{1-15}) acyl; and

the dotted lines indicate optional bonds, with the proviso that the compound is not any one of 20-hydroxy- $14\beta,17\alpha$ -19-norpregn-4-en-3-one, ($3\beta,5\alpha,14\beta,17\alpha$)-pregna-3,20-

20 diol, ($3\beta,14\beta,17\alpha$)-pregna-5,9(11)-dien-3,20-diol, and ($14\beta,17\alpha$)-20-hydroxy-19-norpregn-4-en-3-one.

3. A compound according to claim 2, characterised in that

R_1 is O;

25 R_2 , R_3 , R_5 , R_6 , R_7 , R_9 , R_{10} , R_{11} , R_{12} , and R_{14} all are hydrogen;

R_4 is H or methyl;

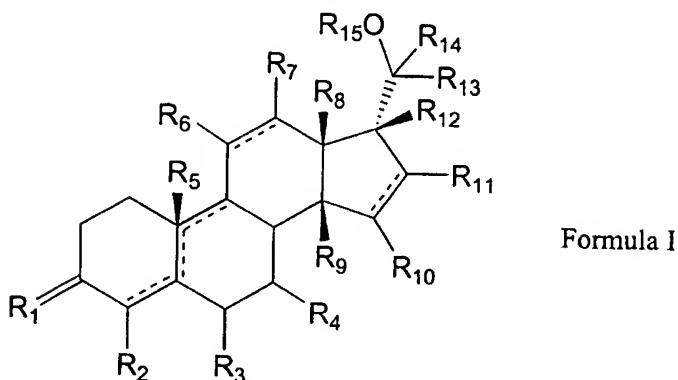
R_8 is methyl;

R_{13} is hydrogen, or C_{1-2} (alkyl) with the configuration at carbon atom no. 20 being S;

R_{15} is H or (C_{1-15}) acyl;

30 and wherein a double bond is present between carbon atoms nos. 4 and 5, and optionally also between carbon atoms nos. 9 and 10.

4. A compound satisfying the structural formula:



wherein

R₁ is O, (H,H), (H,OR), NOR, with R being hydrogen, (C₁₋₆) alkyl, (C₁₋₆) acyl;

5 R₂ is hydrogen, (C₁₋₆) alkyl, or halogen;

R₃ is hydrogen, (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl;

R₄ is hydrogen, halogen, or cyano; or R₄ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₅ is hydrogen, or (C₁₋₆) alkyl;

10 R₆ is hydrogen, (C₁₋₆) alkoxy, or halogen; or R₆ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl, a (C₁₋₆) alkylidene group, or a (C₂₋₆) alkenylidene group, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₇ is hydrogen, or (C₁₋₆) alkyl;

R₈ is (C₁₋₆) alkyl;

15 R₉ is hydrogen, halogen or cyano; or R₉ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₁₀ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₀ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or R₁₀ together with R₁₁ and the carbon atoms at which they are placed form a cyclopropane ring;

20 R₁₁ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₁ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or R₁₁ together with R₁₀ and the carbon atoms at which they are placed form a cyclopropane ring;

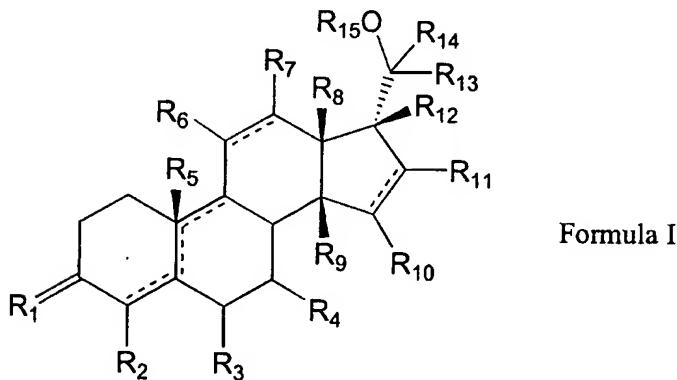
R_{12} is hydrogen, hydroxy, halogen, or cyano; or R_{12} is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, oxo, halogen, or cyano; R_{13} and R_{14} are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, (C_{1-4}) alkoxy, (C_{1-4}) alkyl or halogen; or R_{13} and R_{14} are independently (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{3-6}) cycloalkyl, (C_{5-6}) cycloalkenyl or (C_{2-6}) alkynyl, each optionally substituted by hydroxy, (C_{1-4}) alkoxy, phenyl, oxo, halogen, or cyano; or R_{13} and R_{14} together with the carbon atom at which they are placed form a (C_{3-6}) cycloalkane ring or a (C_{5-6}) cycloalkene ring;

R_{15} is hydrogen, SO_3H , (C_{1-6}) alkyl, (C_{1-15}) acyl; and

10 the dotted lines indicate optional bonds,

for use as a medicine.

5. The use of a steroid compound, or a pharmaceutically acceptable salt or ester thereof, having a hydroxymethyl moiety at carbon atom no. 17, and having a $14\beta,17\alpha$ -configuration, for the preparation of a medicament for treating androgen insufficiency.
- 15
6. The use of a steroid compound, or a pharmaceutically acceptable salt or ester thereof, having a hydroxymethyl moiety at carbon atom no. 17, and having a $14\beta,17\alpha$ -configuration, for the preparation of a medicament for male contraception.
- 20
7. A use according to claim 6 or 7, characterised in that the $(14\beta,17\alpha)$ -17-(hydroxymethyl) steroid satisfies the structural formula:



wherein

25 R_1 is O , (H,H) , (H,OR) , NOR, with R being hydrogen, (C_{1-6}) alkyl, (C_{1-6}) acyl;

R₂ is hydrogen, (C₁₋₆) alkyl, or halogen;

R₃ is hydrogen, (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl;

R₄ is hydrogen, halogen, or cyano; or R₄ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

5 R₅ is hydrogen, or (C₁₋₆) alkyl;

R₆ is hydrogen, (C₁₋₆) alkoxy, or halogen; or R₆ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl, a (C₁₋₆) alkylidene group, or a (C₂₋₆) alkenylidene group, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₇ is hydrogen, or (C₁₋₆) alkyl;

10 R₈ is (C₁₋₆) alkyl;

R₉ is hydrogen, halogen or cyano; or R₉ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

R₁₀ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₀ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or

15 R₁₀ together with R₁₁ and the carbon atoms at which they are placed form a cyclopropane ring;

R₁₁ is hydrogen, (C₁₋₆) alkoxy, halogen, or cyano; or R₁₁ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano; or R₁₁ together with R₁₀ and the carbon atoms at which they are placed form a cyclopropane ring;

20

R₁₂ is hydrogen, hydroxy, halogen, or cyano; or R₁₂ is (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, oxo, halogen, or cyano;

25

R₁₃ and R₁₄ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, (C₁₋₄) alkoxy, (C₁₋₄) alkyl or halogen; or R₁₃ and R₁₄ are independently (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₃₋₆) cycloalkyl, (C₅₋₆) cycloalkenyl or (C₂₋₆) alkynyl, each optionally substituted by hydroxy, (C₁₋₄) alkoxy, phenyl, oxo, halogen, or cyano; or R₁₃ and R₁₄ together with the carbon atom at which they are placed form a (C₃₋₆) cycloalkane ring or a (C₅₋₆) cycloalkene ring;

R₁₅ is hydrogen, SO₃H, (C₁₋₆) alkyl, (C₁₋₁₅) acyl; and

30 the dotted lines indicate optional bonds.

8. A pharmaceutical formulation comprising a compound as defined in any one of the preceding claims, and a pharmaceutically acceptable carrier.
- 5 9. A kit for male contraception comprising means for the administration of a progestagen and means for the administration of an androgen, characterised in that the latter means is a pharmaceutical formulation according to claim 9.

INTERNATIONAL SEARCH REPORT

In. ational Application No

PCT/EP 00/01755

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07J15/00 A61K31/565 C07J53/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. OKADA ET AL: "Synthesis of 3.beta.-hydroxy-5.alpha.-card-20(22)-enolide" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 16, no. 11, 1968, pages 2223-2227, XP002138922 TOKYO JP page 2225 ---	2
X	C. W. SHOPPEE: "Abba des Diginigenins zu einem Kohlenwasserstoff Diginan C21H36" HELVETICA CHIMICA ACTA, vol. 27, 1944, pages 246-260, XP002138923 BASEL CH page 258, paragraph 4 --- -/-	2

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

' Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "S" document member of the same patent family

Date of the actual completion of the international search

29 May 2000

Date of mailing of the international search report

26/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Wachtorn, P

INTERNATIONAL SEARCH REPORT

In national Application No

PCT/EP 00/01755

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ¹	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 277 676 A (AKZO NV) 10 August 1988 (1988-08-10) examples 9,10 ---	1,4,9
A	D. H. BARTON ET AL: "An Approach to the Partial Synthesis of Aldosterone from Steroids Lacking Substitutions at C18" JOURNAL OF THE CHEMICAL SOCIETY., no. 6, June 1957 (1957-06), pages 2698-2706, XP002105693 LETCWORTH GB page 2703, paragraph 6 -page 2704, paragraph 2 ---	2
A	CHEMICAL ABSTRACTS, vol. 53, no. 12, 25 June 1959 (1959-06-25) Columbus, Ohio, US; abstract no. 11442a, A. DA SILVA CAMPOS NEVES: "Study on The Partial Synthesis of Aldosterone" XP002105694 abstract & BOL. ESCOLA FARM. UNIV. COIMBRA, vol. 17, 1957, pages 1-129, ---	2
A	WO 93 15104 A (RES CORP TECHNOLOGIES INC) 5 August 1993 (1993-08-05) page 26; examples 2,3; table 2 ----	1-9
A	US 3 086 027 A (M. PERELMAN ET AL) 16 April 1963 (1963-04-16) column 4, line 61 column 4, line 63 - line 73 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No PCT/EP 00/01755	
Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP 0277676 A	10-08-1988		AT 73137 T AU 603637 B AU 1066988 A CA 1339570 A CN 1030081 B DE 3868647 A DK 30488 A,B, FI 880257 A,B, GR 3004783 T IE 60780 B JP 2664390 B JP 63216895 A KR 9613448 B NZ 223262 A PT 86602 A,B US 5272140 A ZA 8800317 A	15-03-1992 22-11-1990 28-07-1988 09-12-1997 18-10-1995 09-04-1992 24-07-1988 24-07-1988 28-04-1993 10-08-1994 15-10-1997 09-09-1988 05-10-1996 29-08-1989 01-02-1988 21-12-1993 27-07-1988
WO 9315104 A	05-08-1993		US 5264427 A AU 3596893 A	23-11-1993 01-09-1993
US 3086027 A	16-04-1963		OA 3370 A	15-12-1970